Gynecological and dermatological aspects of diagnostics of polycystic ovary syndrome from puberty to menopause

V. G. Siusiuka, M. Y. Sergienko, O. I. Makarchuk, A. O. Shevchenko, O. V. Deinichenko
Zaporizhzhia State Medical and Pharmaceutical University

The article is devoted to the review of scientific publications on gynecological and dermatological aspects of polycystic ovary syndrome (PCOS) in different age periods of women’s life. Analysis of domestic and foreign publications presents that the prevalence of PCOS depends on the age of women and the state of their reproductive function, and is accounted 17% in women 21 to 30 years old and significantly decreased with age. More than half of all cases of endocrine infertility (50-75%) and about 20-22% of the causes of fertile marriage in general are associated with PCOS.

The phenotypic heterogeneity of women with PCOS affects the pregnancy outcomes in different ways, which increases the risk of its pathological course, early pregnancy loss, the development of gestational diabetes mellitus, hypertensive disorders, the birth of small and large for gestational age babies, etc.

“The golden standard” for hyperandrogenism diagnosis in PCOS patients is the determination of the index of free testosterone and androstenedione. Other indicators are important for differential diagnosis and definition of syndrome phenotypes. Different PCOS phenotypes are characterized by different ratios of the contribution of sources of excess androgen synthesis. Depending on the cause, hyperandrogenism in PCOS patients is accompanied by various metabolic risks. Usually, an excess of androgens in women is clinically manifested by hirsutism, seborrheic dermatitis, acne, acanthosis nigricans, and androgenetic alopecia.

The presence of dermatological manifestations of hyperandrogenism has different diagnostic value in puberty, women of reproductive age and in menopause. Acne can be the first sign of pubertal maturation. Additional examinations should be planned in extremely severe cases, which are accompanied by signs of androgen excess, or do not respond to treatment. In women of reproductive age and in perimenopause, the need to assess androgenic status is extremely important. Hair loss according to the female type is associated with manifestations of metabolic syndrome, and it is an independent risk factor for the development of diabetes, atherosclerosis and mortality from cardiovascular diseases.

Therefore it is recommended to use the modified Rotterdam criteria for PCOS diagnosis. Such criteria include clinical or biochemical hyperandrogenism, signs of oligoanovulation, polycystosis (morphology of the ovaries according to ultrasound diagnostics), if other causes of relevant disorders are excluded. At the same time, any two of the specified criteria have diagnostic value, which makes possible to establish not only the diagnosis, but also clinical variant (phenotype) of PCOS, the diagnosis of which is the basis for choosing individual treatment for this contingent of women.

Keywords: polycystic ovary syndrome, pathogenesis, diagnosis, hormones, ultrasound examination, puberty, reproductive age, menopause, age-related changes, skin, hirsutism, acne, alopecia, pregnancy course.
Poly cystic ovary syndrome (PCOS) is a complex polygenic, multifactorial disorder with high heritability [1]. It is considered one of the most common endocrine diseases that affects many women of reproductive age and is a growing problem that, unfortunately, is accompanied by many unwanted complications [1-8]. The spectrum of PCOS manifestations is multifaceted, it is diagnosed not only in women of childbearing age, but also in teenagers and postmenopausal women [4].

The prevalence of PCOS depends on studied population, as well as the definitions used and is within 5–20% [9, 10, 12–18]. The prevalence of PCOS depends on the age and state of reproductive women’s function. According to QiaoWuetal. (2021), it is one in ten women between the ages of 10 and 20, a prevalence rate is 17.23% for women aged 21 to 30 and 9.13% for women aged 31 to 40. The prevalence of PCOS decreases significantly with age and is 2.22% in women aged over 40 years [19, 20].

PCOS is a multidisciplinary problem that requires determination of the severity of clinical manifestations, source and pathogenesis of androgen hyperproduction, an impact on reproductive function, as well as assessment of metabolic and cardiovascular risks [21]. This contingent of women has a significant risk of developing cardiometabolic disorders during their lifetime [22–24].

The frequency of long-term complications in patients with PCOS is 2–6 times higher than in women without this syndrome. Among them are cardiovascular diseases, arterial hypertension, disorders of lipid metabolism, and endometrial cancer [20].

Also, women suffering from PCOS have numerous metabolic risk factors. It is believed that insulin resistance plays an integral role in the pathogenesis of PCOS [25]. In addition to metabolic aspects of the syndrome and fertility disorders, recently more and more studies indicate an increased risk of psychological disorders in women with PCOS [12, 26–31]. PCOS is associated not only with gynecological and dermatological problems, but has a significant impact on the psychosocial aspects of a woman’s life. The disease is accompanied by significant psychological stress, deterioration of well-being, depression, fear about future health and fertility, and accordingly requires a multidisciplinary approach in the management of this contingent of women [32]. PCOS can affect various body systems and be one of the comorbid diseases during a woman’s life due to the wide range of symptoms [33].

Since its discovery (Stein I. F & Leventhal M. L., 1935), PCOS remains a syndrome. No single diagnostic criterion is sufficient for clinical diagnosis. Approaches to diagnosis, treatment and improvement of the quality of life of patients with PCOS are constantly refined and supplemented. Thus, the Rotterdam criteria of 2003 remain the basis for establishing such diagnosis. The relevance of defining syndrome phenotypes was also confirmed [34–36].

PCOS is a heterogeneous condition that has different clinical manifestations and affects health throughout life. Early manifestations occur in childhood and health effects develop throughout adolescence and adulthood [15]. The diagnosis of PCOS is based on clinical, biological and morphological criteria [37]. Because PCOS is a diagnosis of exclusion, standardized criteria have been developed for its diagnosis. The general consensus is that hyperandrogenism is the main feature of PCOS and is associated with a number of physiological dysfunctions [38]. The diagnosis of PCOS is established by two of the three diagnostic criteria in adults (oligo- or anovulation associated with chronic anovulation; clinical and/or biochemical hyperandrogenism; morphology of polycystic ovaries according to ultrasound diagnostics) after exclusion of related disorders of other origins [16, 17, 39–45].

The working group of experts of the US National Institute of Health (NIH), which was based on the methodology of evidence-based medicine data (NIH Evidence-basedMethodologyWorkshop), recommended distinguishing 4 phenotypes of PCOS (clinical variants): phenotype A (classic); phenotype B (incomplete classic); phenotype C (ovulatory); phenotype D (non-androgenic). The diagnosis of PCOS is considered to be «complete» only when its clinical variant is indicated, which is the basis of the choice of individual treatment of a patient [9].

Usually, an excess of androgens in women is clinically manifested by hirsutism, seborrheic dermatitis, acne, and androgenic alopecia [41, 46, 47].

Acne is one of the common dermatological manifestations of PCOS [48]. Thus, clinical manifestations of acne occur in almost every second patient with PCOS [49].

Acne can be the first sign of puberty. History and physical examination are considered the most important components of the evaluation in this age group. Additional tests are usually not needed if there are no signs of androgen excess. PCOS or other endocrine disorders should be considered if acne is extremely severe, accompanied by signs of androgen excess or unresponsive to treatment. Hyperandrogenic conditions in prepubescent children are evidenced by the early appearance of body odor and hair in the armpits or pubes, accelerated growth and maturation of the genitals, and an increase in bone age. After puberty, common signs and symptoms of virilization include infrequent menses, hirsutism, male or female pattern baldness, infertility, polycystic ovaries, clitoromegaly, acanthosis nigricans, and truncal obesity. According to experts, determination of: free testosterone, dehydroepiandrosterone sulfate, luteinizing hormone, and follicle-stimulating hormone may be useful [50].
Acne affects 80% of people between the ages of 11 and 30, however, in adulthood, this problem is more common in women [51].

The pathogenesis of vulgar acne is based on changes in the quantitative and qualitative composition of sebum. It is important that for the steady progress of this disease, it is not an isolated increase in the production of sebum, but a combination of hyperproduction and changes in the lipid profile (decrease in the concentration of linoleic acid, increase in the formation of squalene and saturated fatty acids); skin dysbiosis with the release of virulent subtypes of C. acnes; abnormalities of differentiation and proliferation of keratinocytes in the form of follicular hyperkeratosis; inflammation [52]. Clinically, acne is characterized by the presence of open and closed comedones, papules, pustules, milia and nodules. After the evolution of inflammatory elements (papules, pustules and nodules), post-inflammatory hyperpigmentation, erythema and scars are observed. This, in turn, leads to social maladjustment, depression and anxiety [53].

However, there are no universally accepted visual scores for the assessment of acne, and the Ludwigs visual scale is considered better for the assessment of the degree and distribution of alopecia [16, 41]. Androgenetic alopecia is the most common form of alopecia worldwide [54]. Its pathogenesis is a combination of genetic and hormonal factors [55]. According to the recommendations of the AndrogenExcess and PCOS Society, the term «female pattern hair loss» (FPHL) should be used [56].

Numerous studies have demonstrated the relationship between FPHL, especially with early onset, and metabolic syndrome (obesity, insulin resistance, arterial hypertension, dyslipidemia, etc.) [57, 58]. FPHL is an independent risk factor for the development of diabetes, atherosclerosis and mortality from cardiovascular diseases.

The corresponding shedding is mediated by androgens, as women with signs of hyperandrogenism in PCOS or congenital adrenal hyperplasia often develop an early onset of hair loss. Female pattern hair loss manifests as a decrease in hair density and miniaturization of hair follicles on the crown and frontal part of head, usually with preservation of frontal hairline [56, 59].

It is believed that in women the leading importance is the increase in the levels of androstenedione, dehydroepiandrosterone and free testosterone [60]. Androstenedione, which is mostly produced in ovaries and adrenal glands, is converted to testosterone by 17β-hydroxysteroid dehydrogenase. In this form, it reaches the target tissues. One of the ways of the metabolism of androgens in skin and subcutaneous tissue consists of the transformation into estrogens by aromatization with the help of cytochrome P450 aromatase. Circulating testosterone, or metabolized to dihydrotestosterone (DHT) by the enzyme 5α-reductase, binds to the intracellular androgen receptor (AR) in dermal papilla and hair follicle and is converted to DHT, which has a fivefold higher affinity for the androgen receptors (AR) than testosterone, can activate both the receptor and the expression of the corresponding gene [61, 62].

At present, the role of androgens in pathogenesis of the disease in women is not clearly defined, since only one third of women show abnormal levels of androgens.

The report of the Multidisciplinary Committee on Hyperandrogenism and Polycystic Ovary Syndrome on Acne and GA in Adult Women (2022) notes disagreement with the recommendations of dermatological clinical guidelines regarding acne as a predominantly inflammatory process and asserts the need to assess androgen status in all women with acne [63].

In addition, estrogen plays a protective role in hair growth, as evidenced by an increase in prevalence of hair loss during the typical female menopause period, lengthening the anagen phase during pregnancy, etc. [64]. The effect of androgens on hair follicles depends on local bioavailability, but not on blood levels. The skin is a peripheral organ of androgen metabolism. Sebocytes synthesize testosterone from adrenal precursors and are also able to inactivate them together with keratinocytes, thus playing an important role in androgen homeostasis [55]. Although acne and female pattern hair loss are common complaints in patients with PCOS, data do not currently support their use as reliable diagnostic markers of PCOS [41]. When evaluating hirsutism, preference is given to standardized visual scales, such as the modified Ferriman-Gallway (mFG) scale, which remains the gold standard for the assessment of clinical hyperandrogenism [16, 17, 41]. The threshold value used for «abnormal» can vary depending on a patient population from ≥4 to ≥8 [41].

Acanthosis Nigricans is usually combined with manifestations of hirsutism and insulin resistance in PCOS. It is characterized by the presence of velvety hyperpigmented skin areas in the neck and armpits. It is observed in 5% of women with hyperandrogenism [65, 66].

In turn, postmenopausal hyperandrogenism is a state of relative (physiological) or absolute excess of androgens and is dermatologically manifested by acne, hirsutism and androgenetic alopecia. The most common cause of hyperandrogenism in premenopausal women is PCOS. Both adrenal and ovarian androgen levels continue to be higher in postmenopausal women with PCOS than in women without PCOS [67, 68].

In women, androgens are normally functioning to maintain bone density, muscle mass, and sexual function [41]. Ovaries, adrenal glands and peripheral tissues play a key role in androgen metabolism in women [46]. The classical effect of androgens on target organs is carried out through androgen receptors, which regulates the transcription of the nuclear receptor gene. However, the androgen-androgen receptor complex can also interact directly with membrane proteins or signaling molecules for more rapid effects [69]. Androgenic precursors such as dehydroepiandrosterone (DHEA), its sulfated ester DHEAS and androstenedione (AnD) are secreted by the zona reticularis of adrenal cortex and activated to more potent androgens such as testosterone (T) and dihydrotestosterone (DHT).

However, it is androgenic precursors such as DHEA and AnD that can undergo activation to more potent active androgens such as T and DHT in the periphery,
depending on the expression of androgen-activating enzymes in local tissues [46]. AndD is a weak androgen precursor that circulates in higher nanomolar concentrations than serum T and therefore may have increased diagnostic utility in screening women with androgen excess. Unlike T, AndD is not affected by sex hormone-binding globulin (SHBG) levels, and therefore may be a more reliable marker of androgen excess associated with PCOS [46, 70]. Calculated free testosterone, free androgen index or calculated bioavailable testosterone should be used to assess biochemical hyperandrogenism in the diagnosis of PCOS. AndD and DHEAS may be considered if total or free testosterone is not elevated.

PCOS is traditionally associated with ovarian hyperandrogenism (HA), however, in various phenotypic forms of PCOS, both ovarian and adrenal components are observed: transport (due to low levels of sex steroid-binding globulin (SBG)) and peripheral (synthesis of active androgens in skin and adipose tissue). Different phenotypes of PCOS are characterized by different ratios of the contribution of sources of excess androgen synthesis. Depending on the source, HA in PCOS is accompanied by different metabolic risks. For example, women with PCOS with a predominance of adrenal HA have lower metabolic risks. The role of tissue-specific androgen metabolism and the impact of adipokines and hepatokines on it [71].

The approach recommended by certain clinical guidelines not to evaluate biochemical HA in severe manifestations of clinical HA is outdated. The question of a clinical significance of biochemical HA in the absence of unexpressed clinical HA is controversial. Almost all modern studies confirm that it is necessary to take into account not only biochemical HA, regardless of the presence of clinical HA, but also which forms of androgens are increased and to what extent, because this can affect the presence and prognosis of reproductive and metabolic risks [71–73].

It should be noted that the interpretation of androgen levels should be based on reference ranges of laboratory used, recognizing that ranges for different methods and laboratories vary widely [16, 17, 41]. It is also recommended to stop taking drugs three months or longer before measurement when evaluating biochemical hyperandrogenism in women using hormonal contraception [16, 17].

Impaired glucose metabolism is one of the links in the pathogenesis of PCOS. Hyperinsulinemia (HI) and insulin resistance provoke hyperandrogenemia and even deeper ovulation disorders. Insulin and androgens act as inducers of the early stages of folliculogenesis, so their excess concentration leads to the activation of a large number of antral follicles, which lack the capacity of follicle-stimulating hormone for full maturation [74].

When considering the problems of hyperandrogenism, clinical and biochemical manifestations of PCOS, one should dwell on the issues of insulin resistance (IR), since the disease can develop both on the background of IR and without it.

Compensatory hyperproduction of insulin is formed in the woman’s body in the first option. The increased level of insulin, in turn, leads to an increase in the secretion of androgens. In the second variant, the level of insulin in blood is normal, but there is a violation of sensitivity of ovarian receptors to insulin, which leads to the same consequences [75].

According to Viesich T.L. et al. (2021) hormonal secretion and biochemical indicators of women depend on the presence of metabolic syndrome [75]. The latter have shown moderate hyperprolactinemia, a decrease in the level of somatomedin-C against the background of IR. In women with PCOS without metabolic disorders, moderate HA hyperandrogenism comes to the fore.

Anti-Mullerian hormone (AMH) is not included in the diagnostic criteria for PCOS and should not be used as an alternative to ultrasound evaluation of polycystic ovary morphotype according to current guidelines [76, 77]. However, the assessment of the level of AMH can increase the effectiveness of PCOS diagnosis, especially its C and D (normoandrogenic, ovulatory) phenotypes, provided that clinical data, indicators of gonadotropins, androgens, and sex steroid-binding globulin are taken into account [78, 79].

Mean AMH levels are known to be higher in women of reproductive age with PCOS compared to women without PCOS. Menopause occurs later in PCOS patients, and there are also observations of improvement in fertility with age, which can be explained by the normalization of previously high levels of AMH and the corresponding restoration of folliculogenesis [80, 81]. Today, AMH is considered as one of the key factors of folliculogenesis disorder in PCOS. Chronically high levels of it make it impossible for primary follicles to grow, instead a large number of follicles with a diameter of 2–6 mm persist. It is they who provide chronically high concentrations of AMH, closing a vicious circle [82, 83]. Recently, another hypothesis was proposed regarding the involvement of AMH in the pathogenesis of PCOS: acting on AMH receptors in Gonadotropin-Releasing Hormone (GnRH) neurons, AMH leads to increased activity of the GnRH pulse generator and, accordingly, increased levels of luteinizing hormone [84, 85].

A common feature of PCOS is infertility with 75–80% of these women suffering from infertility due to anovulation [86, 87, 88]. Ovulatory dysfunction is associated not only with infertility, but also with an increased likelihood of endometrial hyperplasia and endometrial cancer [42]. The diagnosis of PCOS should be considered and evaluated according to the recommendations in the presence of irregular menstrual cycles. Oligoamenorrhea (interval between cycles > 35 days or <8 cycles per year) can be used as a marker of ovulatory dysfunction for the diagnosis of PCOS [41]. Ovulation can be confirmed in individuals with an uncertain menstrual history by serum progesterone or luteinizing hormone [16, 41].

PCOS accounts for more than half of all cases of endocrine infertility (50–75%) and about 20–22% of infertile marriage causes in general [89]. About 80% of all cases of anovulatory infertility are related to PCOS. In addition, 42–73% of women with PCOS have a high probability of spontaneous abortion [19, 90].
Phenotypic heterogeneity of women with PCOS affects pregnancy outcomes differently. Problems with conception can result from obesity, metabolic dysfunction including (IR), inflammation, or endocrine abnormalities. These conditions affect ovulatory function, endometrial sensitivity and oocyte quality [91].

Pregnant women with PCOS have an increased risk of a pathological course of pregnancy regardless of infertility presence in anamnesis and the use of assisted reproductive technologies [92]. It includes early pregnancy loss, development of gestational diabetes mellitus (GDM), disorders of the hypertensive spectrum (gestational hypertension and preeclampsia), birth of small and large-for-gestational-age babies, premature pregnancy and cesarean section [93, 94]. Pre-pregnancy body mass index associated with the absolute risk of many important obstetric outcomes, including preeclampsia, gestational diabetes, indicated preterm delivery, macrosomia [95].

The results of a recent meta-analysis showed an association of PCOS with an increased risk of preterm birth [92, 93].

It is important that the period before conception opens a window of opportunity for preventive examination and safe treatment the result of which will be the normalization of menstrual cycle, the improvement of somatic health of a woman, the quality of the oocytes and endometrium, and the potential results of pregnancy.

Ultrasonic scanning of ovaries has one of the decisive values for the evaluation of patients with suspected PCOS. The main ultrasound features are the determination of ovarian volume and the number of antral follicles [96]. In the International evidence-based guideline for the assessment and management of polycystic ovary syndrome, based on actual data, the criteria for diagnosis based on the results of ultrasound diagnostics (USD), using the latest technology of transvaginal ultrasonography with a sensor frequency of 8 MHz or more, the number of follicles should be ≥20 follicles per ovary and/or the volume of any ovary ≥10 cm³, ensuring the absence of corpora lutea or dominant cysts follicles [16, 17, 34]. Studies to assess ovarian morphology should be performed in the early follicular phase. In addition, USD allows to examine the state and thickness of endometrium to exclude hyperplastic processes, endometrial cancer against the background of hyperestrogeny, as well as to determine the indications for hysteroscopy and endometrial biopsy [9].

Women with oligo- or amenorrhea are recommended to perform ultrasound between the 3rd and 5th days after progesterone-induced bleeding [96]. Also, the use of oral contraceptives in the anamnesis should be taken into account, since they lead to a decrease in the size of the ovaries, and in women who take them, the specified criteria are unreliable [9, 96]. A serum level of anti-Müllerian hormone should not be used as an alternative to detect PCOS or as the sole test for its diagnosis [16, 34].

The evaluation for PCOS in adolescent girls and postmenopausal women is of particular note. Diagnosis of PCOS in adolescence still raises many questions. The problem is that the characteristics of normal puberty often coincide with the symptoms of PCOS [44, 97]. The diagnostic criteria for adolescent PCOS were derived from adult criteria, which complicates the diagnosis because the criteria include normal physiological changes that occur during puberty, such as acne, hirsutism, menstrual irregularities, high androgen levels, and polycystic ovary morphology [98].

Therefore, USD is not used as a criterion for the syndrome in the first 8 years after menarche due to the high frequency of multifollicular ovaries in adolescence and, accordingly, low specificity. To clarify the diagnosis in such cases dynamic observation is required, i.e. repeated examination with repeated evaluation of the results. Adolescents who do not fully meet the diagnostic criteria may be identified as «high risk» or «risk group» for the development of PCOS. Such patients should be re-evaluated after the completion of puberty or 8 years after menarche [6, 11, 16, 17, 39, 44, 99].

It is the peculiarities of hormonal homeostasis and metabolism in adolescence that create prerequisites for overdiagnosis of PCOS. In teenage girls, in the presence of a menstrual cycle disorder and hyperandrogenism, it is possible to consider PCOS (Phenotype B), respectively, without taking into account ultrasound signs [100]. Although pelvic ultrasonography is not indicated for the diagnosis of PCOS in adolescents. It can be used to investigate other possible uterine or ovarian abnormalities in adolescent girls, for example, with primary amenorrhea [99].

Persistence of PCOS in postmenopause can be considered probable if there are persistent signs of hyperandrogenism. A diagnosis of postmenopausal PCOS may be supposed if there is a past diagnosis of PCOS, a long history of irregular menstrual cycles and hyperandrogenism, and/or PCOS during reproductive years. Postmenopausal women with new severe hyperandrogenism or worsening hyperandrogenism, including hirsutism, should be evaluated to rule out androgen-secreting tumors and ovarian hyperthecosis [16, 17]. The presence of polycystic ovaries in postmenopausal women correlates with increased concentrations of testosterone and triglycerides in blood serum [96].

Therefore, the analysis of domestic and foreign publications shows that it is recommended to use the modified Rotterdam criteria in the diagnosis of polycystic ovary syndrome. Such criteria include clinical or biochemical hyperandrogenism, signs of oligoanovulation, polycystosis (morphology of the ovaries according to ultrasound diagnostics), provided that other causes of relevant disorders are excluded. At the same time, any two of the specified criteria have diagnostic value, which allows establishing not only the diagnosis, but also the clinical variant (phenotype) of polycystic ovary syndrome, the diagnosis of which is the basis for choosing individual treatment for this contingent of women.
REFERENCES


