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Pediatric Endocrinology Update
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Review

Polycystic ovarian syndrome in adolescents: from diagnostic criteria to therapeutic management

Nicolas C. Nicolaides[1,2,3], Andreas Matheou[4], Florentia Vlachou[5], Vassos Neocleous[6], Nicos Skordis[6,7,8]

[1]Division of Endocrinology, Metabolism and Diabetes, First Department of Pediatrics, National and Kapodistrian University of Athens Medical School, "Aghia Sophia" Children's Hospital, Athens, Greece; [2]Division of Endocrinology and Metabolism, Center of Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece; [3]University Research Institute of Maternal and Child Health and Precision Medicine, and UNESCO Chair on Adolescent Health Care, National and Kapodistrian University of Athens, "Aghia Sophia" Children's Hospital, Athens, Greece; [4]Manchester Medical School, University of Manchester, United Kingdom; [5]Barts and the London School of Medicine and Dentistry, Queen Mary University of London, United Kingdom; [6]Department of Molecular Genetics, Function and Therapy, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus; [7]School of Medicine, University of Nicosia, Nicosia, Cyprus; [8]Division of Paediatric Endocrinology, Paedi Center for Specialized Pediatrics, Nicosia, Cyprus

Summary. Polycystic ovarian syndrome is a common endocrinologic condition diagnosed in women of childbearing age. It is primarily associated with androgen excess and ovarian dysfunction, which contribute to menstrual irregularity, oligo-anovulation, infertility, hirsutism and acne. It is associated with several systemic conditions, including type 2 diabetes mellitus, cardiovascular disease, obesity and neuropsychological disorders. The exact pathophysiology and clinical features are highly variable and, thus, there is still controversy in defining the diagnostic criteria. In this review, we outline the main diagnostic criteria, discuss the mechanisms involved in the complex pathogenesis, and present the associated clinical manifestations and therapeutic management of the syndrome in adolescents. (www.actabiomedica.it)

Key words: adolescents, hyperandrogenism, insulin resistance, ovarian dysfunction, polycystic ovarian syndrome

Introduction

Polycystic ovarian syndrome (PCOS) is reported to affect 6-10% of women of reproductive age and is considered as the most common endocrinologic condition in this patient group (1, 2). The highly complex pathophysiology, the variable clinical presentation and the lack of adequate evidence-based data contribute substantially to this wide prevalence rate, as several diagnostic guidelines are currently in use. Even though these diagnostic criteria differ in application, there is a consensus that this syndrome is primarily characterized by the presence of hyperandrogenism and ovarian dysfunction (3). The main features include menstrual irregularity, oligo-anovulation, infertility, as well as hirsutism, acne and polycystic ovarian morphology on ultrasonographic imaging (4). Defining the syndrome in adolescents proves to be even more challenging than in adults, as the majority of the reproductive symptoms occur as part of the expected physiological hormonal imbalance of puberty (5). The aetiogical causation behind PCOS is yet to be precisely defined, but it is evident that familiar genetic predisposing factors interact with environmental stimuli both *in utero* and in pre-pubertal life. The main implicating pathophysiological features include insulin resistance and primary ovarian dysfunction, which consequently contribute to both the dysregulation of the reproductive system and the increased likelihood of developing systemic conditions, such as obesity, type 2 diabetes mellitus,

cardiovascular disease, and neuropsychological disorders (6). Management focuses on both improving the reproductive symptoms, especially infertility and menstrual irregularity, as well as the metabolic complications which when left untreated can lead to multiple systemic comorbidities (7). This review aims to outline the current diagnostic criteria for PCOS, describe the pathogenetic mechanisms, and present the clinical features. Finally, management options are explored and compared for their efficacy.

Diagnostic criteria

PCOS was first described in literature by Stein and Leventhal in 1935, who reported a series of seven female patients presenting with amenorrhea or oligomenorrhea, sterility, obesity and hirsutism. Interestingly, the majority of them had polycystic ovaries. The authors suggested the utilization of pneumoentgenographic imaging as a diagnostic tool for patients with similar presenting complaints. Diagnosis was confirmed when the size of ovaries was at least 75% of the size of the uterine body, while it was refuted when the size was less than 25% of it (8).

In 1990, a panel of experts discussed the requirements for defining PCOS and set the NIH criteria. According to them, for a patient to be diagnosed with this syndrome, two conditions are required to be met: evidence of clinical or biochemical androgen excess and oligo-anovulation (9). This definition is essentially a diagnosis of exclusion, as it necessitates the absence of all other endocrinological aetiologies associated with hyperandrogenism (3, 10). In 2003, the presence of polycystic ovarian morphology on ultrasonographic imaging was added as the third defining condition of the syndrome. Therefore, diagnosis is considered valid if two out of the three criteria are met, in the absence of other endocrinological conditions. The so-called "Rotterdam Criteria" were endorsed by both the European Society of Human Reproduction and Radiology (ESHRE) and the American Society for Reproductive Medicine (ASRM) (11, 12). In 2006, the Androgen Excess and PCOS Society (AE-PCOS) suggested that PCOS is primarily associated with androgen excess. Thus, the diagnosis necessitates the presence of hyperandrogenism (clinical or biochemical) with signs of ovarian dysfunction, in the absence of other endocrinological aetiologies (13) (Table 1).

To prevent any further confusion over the classification of the syndrome that influenced patient management in a negative fashion, an updated NIH workshop endorsed the use of the Rotterdam criteria for diagnosis and provided an additional requirement. Clinicians were prompted not only to diagnose patients based on the guideline, but also to provide a phenotypic description of each patient, which would fit in one of four possibilities: Phenotype A includes patients with all three characteristic findings, while phenotype B and C involve the presence of androgen excess with only one other feature, namely ovarian dysfunction and polycystic ovarian morphology respectively. Lastly, phenotype D describes patients having both ovarian dysfunction and polycystic ovaries without hyperandrogenism (14) (Table 1).

The aforementioned guidelines for adults form the basis for the diagnosis of PCOS in adolescents. However, the defining characteristics of PCOS in this patient group prove to be particularly challenging because the typical presentation of hyperandrogenism and oligo-anovulation occur naturally as part of the physiological process of puberty (15). Indeed, clinical manifestations of androgen excess, such as hirsutism and acne, are commonly observed in healthy adolescent girls. Additionally, irregularity in the menstrual cycle during the first two years after menarche is considered physiological, as the hormonal changes governing reproductive maturation take time to normalise (16). The utilisation of ultrasonographic imaging for the assessment of ovarian morphology can be controversial, since both the size and volume of the adolescent ovaries are larger than the ones seen in adults (17). Previous research revealed that 26% of girls undergoing puberty demonstrate evidence of multiple ovarian follicles (18), which in an adult would indicate PCOS. Therefore, the diagnostic guidelines for adults have been insufficient in defining the syndrome in adolescents.

To develop a consensus regarding the diagnostic classification of PCOS in adolescents, the Paediatric Endocrine Society in cooperation with ESHRE, ASRM and the Australian National Health and

Table 1. The 4 main diagnostic guidelines for PCOS in adults

Diagnostic guideline	Clinical presentation			Practical notes
	Hyperandrogenism (clinical or biochemical)	Oligo-anovulation	Polymorphic ovarian morphology	
NIH 1990	+	+	N/A	Both features and exclusion of other aetiologies are required.
Rotterdam 2003	+/ -	+/ -	+/ -	2 out of 3 diagnostic features are required and exclusion of other aetiologies.
AE-PCOS 2006	+	+/-	+/ -	Hyperandrogenism is required with one or both of the others and exclusion of other aetiologies.
Revised NIH 2012	+/ -	+/ -	+/ -	2 out of 3 features and exclusion of other aetiologies are required. Phenotypic characterisation is also needed: (A) All 3 features (B) Hyperandrogenism + oligo-anovulation (C) Hyperandrogenism + polycystic ovarian morphology (D) Oligo-anovulation + polycystic ovarian morphology

Medical Research Council (NHMRC) concluded that PCOS should be suspected when adolescents present with irregular menstrual cycles (5). It should be noted that in adolescents with regular menstrual patterns, PCOS is still a possibility, which is addressed by measuring progesterone levels that might indicate anovulation. A second criterion endorsing this diagnosis is evidence of biochemical and clinical androgen excess. The former is suggested to be assessed by measuring the levels of free testosterone, androgen index or bioavailable testosterone. Care should be taken to exclude any other endocrinologic conditions associated with hyperandrogenism (19). The latter is established by the presence of hirsutism, alopecia, or excessive acne. The proposed classification systems of hirsutism and alopecia are the modified Ferriman Gallwey and Ludwig scores respectively. Assessment of ovarian characteristics using ultrasound imaging is not endorsed due to the physiological presence of multiple follicles on the adolescent ovaries. Transvaginal ultrasound is the preferred modality to investigate the possibility of PCOS in sexually active adolescent girls. PCOS is considered the likely diagnosis when the volume of each ovary is ≥10ml and the follicle count is ≥12 (20).

Pathophysiology

The pathophysiology of PCOS is still not fully understood. The aetiological justification of the clinical presentation was proven to be multifactorial, involving the interaction of genetic, epigenetic, endocrine and environmental factors. Nevertheless, the existing evidence-based data suggest that insulin resistance and androgen excess are the principal pathological features responsible for the phenotypic characteristics of PCOS (21-23).

Endocrine factors (Figure 1)

Insulin resistance is a commonly observed feature in patients with PCOS. Evidence suggests that it occurs independently of the pre-existence of high body mass index (24). Adolescents display higher lev-

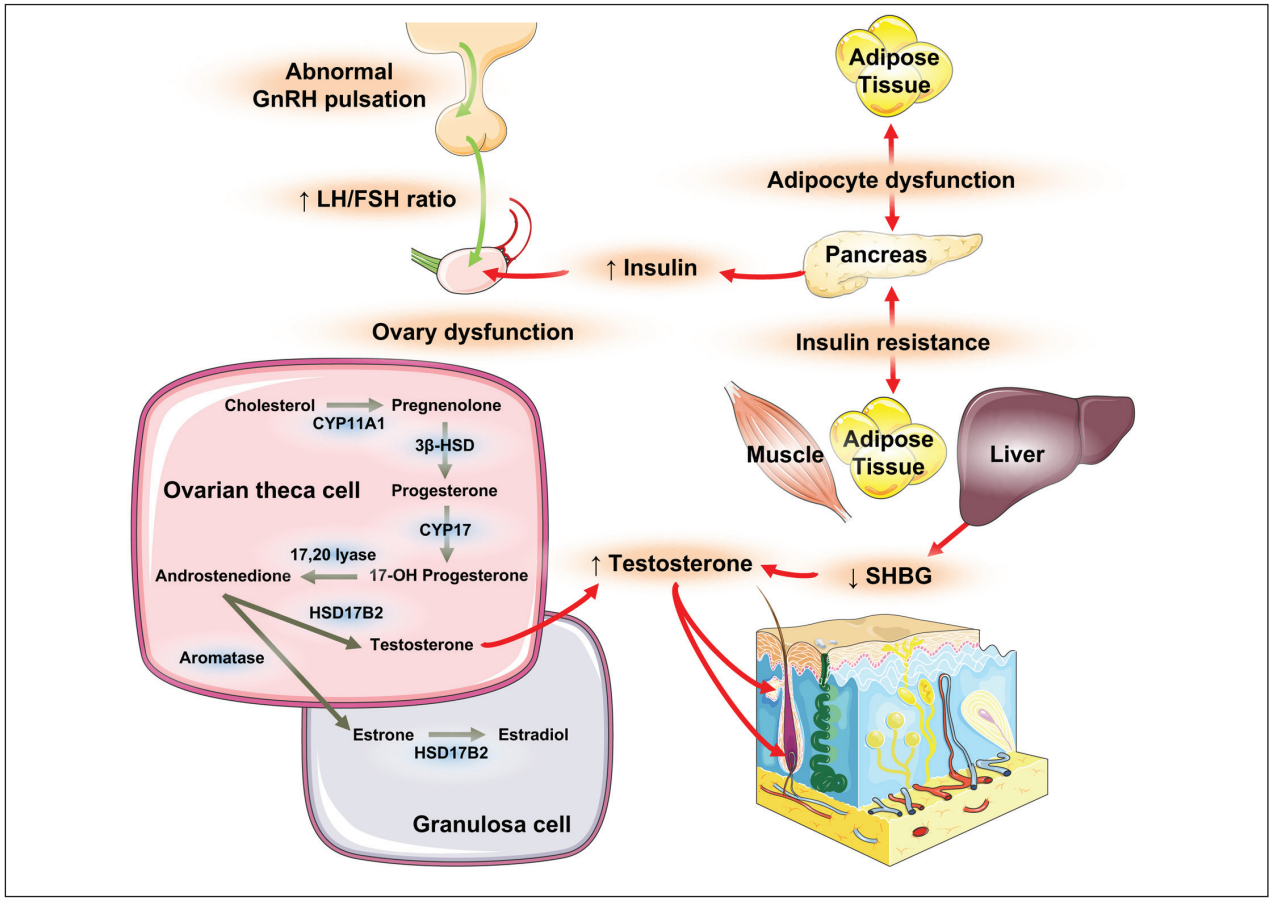

Figure 1. The complex pathophysiology of PCOS

els of growth hormone and insulin-like growth factor 1 (IGF-1) (25), both of which are thought to mediate insulin resistance, which tends to be tissue selective. Liver, adipose and skeletal muscle tissues are often less sensitive to insulin, while the adrenals and ovaries experience the reverse (26). Both the increased insulin activity and the elevated IGF-1 were demonstrated to promote androgen synthesis by enhancing the production and action of LH (27). Conversely, the diminished responsiveness of the liver to insulin hinders the production of sex hormone binding globulin (SHGB), thereby increasing the peripheral androgen concentration (28). Ovarian steroid synthesis is further promoted by insulin resistance that was shown to enhance the activity of the cytochrome enzymes (P450c17 and P450scc) (22, 29).

Obesity is observed in 40-80% patients with PCOS and it is thought to be related in the pathophysiology of the syndrome (30). Menstrual irregularity and excessive androgen production are closely associated with obesity. The elevated levels of adipose tissue seen in obese patients contributes to exacerbation of insulin resistance and to the reduction in SHGB, both of which subsequently upregulate the production of androgens. Adipose tissue contains key enzymes involved in steroid synthesis, which further stimulates androgen secretion (31, 32).

In adolescents with PCOS the delicate balance of hormones cannot be maintained, as the grossly elevated LH stimulates excessive productions of androgens, which fail to be adequately converted to oestrogens. The diminishing concentration of FSH in combination with the insufficient oestrogen production, fails to support the maturation of a dominant follicle, resulting in anovulation, and thus menstrual irregularity (33). Moreover, the elevated LH production stimulates the

theca cells in the ovaries to trigger the synthesis of the enzymes P450scc, P450c17, and 3βHSD which further increase androgen secretion (34). Furthermore, the diminished FSH reduced the conversion of the androgen to oestrogen and thus maturation is halted for the plethora of underdeveloped follicles. These follicles are characterised by thecal proliferation and fluid collection, both of which result in the characteristic polycystic morphology (35). This process is further exacerbated in the presence of hyperinsulinemia. Additionally, it was shown that AMH levels were 2-3 times more elevated in patients with PCOS compared to health individuals, which further contributes to follicular arrest, anovulation and thus menstrual irregularities.

The typical presentation of androgen excess is partly attributable to changes in the physiological pulsatile release of the hypothalamo-pituitary hormones, which are implicated in steroid synthesis and follicular maturation (36, 37). As mentioned above, LH levels increase while FSH concentration is diminished, leading to an elevation of the LH:FSH ratio (36, 38). GnRH is also implicated in this dysregulation of the negative feedback system, as the frequency at which it is secreted was observed to be higher. The increased GnRH correlates with a selective increase in LH, which is consistent with the biochemical features in PCOS (39). The altered GnRH physiological cycle is closely related to hyperinsulinemia and hyperandrogenaemia, since the latter is likely to cause the former. Of note, GnRH secretion can be also modulated by kisspeptins, which are hormones produced in the hypothalamus and significantly contribute to the negative feedback system involved in the hypothalamic-pituitary-gonadal axis (40). Specifically, the tight balance between neurokinin B (excitatory kisspeptin) and dynorphin (inhibitory kisspeptin) allows the pulsatile GnRH, LH and FSH to be appropriately regulated. In the absence of androgens, kisspeptins upregulate GnRH secretion, while in excess the reverse occurs. The role of these hypothalamic hormones for PCOS is still not confirmed, as preclinical trials demonstrate both a normal physiological response as well as dysregulation of the negative feedback system in the presence of hyperandrogenism (6, 21).

Pre-clinical studies performed on mice have suggested that the neurotransmitter gamma-aminobutyric acid (GABA) pathway might be implicated in the pathogenesis of PCOS. The activation of the GABA-A receptors mediate an increase in the GnRH secretion and the consequent elevation in LH and androgens (41). PCOS mice models were shown to further drive the GABA and thus GnRH stimulation when exposed to dihydrotestosterone and its metabolic by-products (42). Further research is required to establish the relationship of GABA and GnRH pulses.

Genetics

The pathogenesis of PCOS might be partly attributed to genetic alterations, which have been endorsed by genome wide association, twin as well as linkage studies (43). The cytochrome P450 group of enzymes play a vital role in the process of steroid synthesis, and thus any alterations in the genes encoding for them can be associated with PCOS (44). Indeed, it was noted that in patients with PCOS the expression of *CYP11A1* gene is upregulated in the theca cells, and thus androgen production is elevated. The presence of the pentanucleotide repeat (TTTTA) was positively correlated with PCOS. This polymorphism was also linked to obesity and lower FSH levels (43). Moreover, the most common allelic alteration in the *CYP17* gene associated with PCOS was demonstrated to enhance the PCOS phenotype (45). Furthermore, in PCOS the *CYP19* gene is downregulated leading to reduced aromatase activity, which consequently contributes to androgen excess (46). In addition, the androgen receptor gene was shown to be less expressed in PCOS patients, thereby reducing the available receptors for androgens. This is therefore translated into lower uptake and greater free circulation of androgens (47). In the past *SHBG* gene polymorphisms have also been shown to be implicated when present in PCOS patients with the reduction in gene expression, resulting in the higher circulating androgen concentration (48). Recently, an important report by Dapas et al. (49) that performed a clustering analysis of 893 women with PCOS, using reproductive and metabolic traits identified distinct metabolic subtypes and novel genetic variants uniquely associated with each of the PCOS subtypes. Consequently, this is suggestive of the existence of distinct forms of PCOS that are as-

sociated with different underlying biological mechanisms.

Epigenetics

The combination of genetic with environmental factors in the pathogenesis of PCOS is evident and thus epigenetic stimuli can significantly affect the phenotype seen in patients. These are factors which affect the phenotypic expression of genes without causing any mutations in the DNA sequence (4). Representative examples include factors affecting fetal and child development, dietary components or even cytotoxic exposures in the form of chemicals or drugs (50). A theory suggests that fetal exposure to elevated blood pressure, diabetes or smoking can diminish growth, which in turn leads to the expression of the "thrifty genes" (51). Babies with these genes are thought to be more likely to have insulin resistance, hypertension, androgen excess, or PCOS when they reach adolescence (52). Even though this predisposition exists, individuals with additional environmental contributors, such as poor diet and lack of exercise, are more likely to develop metabolic syndrome and PCOS. It was also proposed that the presence of maternal androgen or glucocorticoid excess *in utero* can generate symptoms in PCOS later in life (53).

Environmental factors

Endocrine-disrupting chemicals (EDC) describe any substance that the patients are exposed to and it is able to negatively modulate the normal metabolic and hormonal mechanisms. Their interplay with genetic components as well as lifestyle factors can affect the pathophysiology of PCOS (54). Processed food can be considered as an EDC, as certain nutritional components enhance the effects of insulin and insulin resistance in patients with PCOS. Gluten, found in many starch-based foods, can modulate the endocrine system by either the production of plant-based oestrogen or through pesticide release during farming, which is thought to affect androgen and oestrogen production (55). An additional food group affecting the PCOS phenotype is dairy products, which can promote insulin resistance and disruption in oestrogen and testosterone (56). The role of starch-based and dairy products in PCOS is further emphasised by data suggesting an improvement in insulin resistance and androgen excess when such food groups are discontinued (57). Other environmental chemicals include certain pharmaceutical drugs such as β-blockers, phytosterols and lipid-modulating agents (58). Finally, bisphenol A, a substance commonly found in plastic, has been recognised as a mediator of androgen excess, especially when patients come in contact with it in infancy (59).

Clinical manifestations

Androgen excess is observed in 80% of patients with PCOS presenting with hirsutism, alopecia or acne (60). Hirsutism, which is described as the presence of excess amount of terminal hairs, is more commonly observed in the lower half of the face, specifically the chin, neck and sideburns. Also, it is sometimes seen in the abdomen, lower back, inner thighs and around the gluteal region. The gradual development of hirsutism is positively correlated with an increase in weight (61). Clinically, the severity of this feature can be assessed using the modified Ferriman Gallwey scoring system, which involves the evaluation of eleven different locations on the body for the presence of hirsutism. A score of 1-4 is given for each of these body parts, with 1 denoting lack of visible terminal hair growth and 4 indicating excessive hirsutism. If the resulting score is greater than 8, then hirsutism is present (60, 62). Alopecia, caused by hyperandrogenism, resembles male-like hair loss, mainly found in the vertex, crown or even in the frontal and temporal skull (62). While acne is closely associated with hyperandrogenism, it is not considered a defining feature of PCOS when it presents alone due to its common manifestation physiologically in puberty. However, sudden onset of acne in adulthood or acne, which is unresponsive to topical agents, is more likely to be associated with PCOS (63).

Ovarian dysfunction is another major factor associated with the PCOS phenotype. Clinically it manifests in variable degrees of menstrual irregularity, which can be subjective, as this feature is also common as part of the normal physiological pubertal changes. However, even though this irregularity is common in

puberty, it still resembles adult menstrual patterns. Specifically, approximately 75% of adolescent cycles are reported to be 21-45 days in duration in the first year post menarche, and is expected to reach adult duration 2-3 years after commencement of menstrual cycles. Therefore, menses which occur as frequently as up to 19 days after the previous menstruation or as rarely as more than 90 days after the latest period make the PCOS diagnosis more likely (19). Irregular menstrual pattern reflects anovulation, the persistence of which is indicating PCOS. Table 2 depicts the variable presentation of irregular menstrual patterns aiding in the PCOS diagnosis (5). In adulthood, patients may present with difficulty in conceiving a child or completing a pregnancy to term, as reflected by the reported 30-50% miscarriage rate. This can be explained by the follicular arrest and the absence of a dominant follicle for ovulation (63).

Biochemical and imaging findings

In the presence of clinical suspicion of hyperandrogenism, biochemical measurements of circulating androgens can endorse the PCOS diagnosis. The recommended hormones to be measured are total and free testosterone, with the latter being the most sensitive as it is not bound on the SHBG and it freely circulates. The test is considered positive when the detected values are above the normal thresholds of each hormone, which are subject to the process used and individual laboratory (15).

Polycystic ovarian morphology is consistent with the diagnosis of PCOS and is based on transvaginal ultrasonographic imaging results. An ovarian volume of ≥10 ml and the presence of ≥12 antral follicles with a diameter of 2-9 mm is consistent with PCOS. However, care should be taken when assessing ovarian morphology in adolescents as the majority of patients would fulfil these criteria due to physiological pubertal changes (5).

Differential diagnosis

Given the complexity of the endocrinologic and metabolic pathways involved in the pathogenesis of PCOS, the diagnostic characteristics described above can fit in several pathologic conditions. The differential diagnosis of PCOS include hypothyroidism, congenital adrenal hyperplasia (CAH), Cushing's syndrome and hyperprolactinemia. The patient history, physical examination as well as biochemical and imaging results should be addressed in such way that these alternative diagnoses are excluded. This is in line with any of the existing diagnostic guidelines, according to which PCOS is determined by ensuring the absence of any other endocrinological aetiologies (64).

The common clinical features observed in both PCOS and hypothyroidism include various menstrual irregularities and abnormalities in uterine bleeding. To exclude hypothyroidism, the physician is required to measure the TSH levels in the patient, the value of which would be normal in PCOS and significantly

Table 2. Irregular menstrual patterns in adolescent patients (5)

Type of irregular uterine bleeding	**Definition of menstrual irregularity**
Primary amenorrhea	Absence of menses at 15 or 3 years after breast development
Secondary amenorrhea	>90 days of lack of menorrhea after menarche
Oligomenorrhea • **<1 year post-menarche** • **>1 - <3 year post menarche** • **>3 years post menarche**	• Any irregularity is normal • Menses experienced <21 and >45 days after the last period or <4 cycles/year • Menses experienced <21 and >35 days after the last period or <8 cycles/ year
Excessive anovulatory abnormal uterine bleeding	Menorrhea occurring in <21 days or having a duration of >7 days

increased in hypothyroidism. In both Cushing's syndrome and congenital adrenal hyperplasia (CAH) the resulting characteristic finding is a state of over secretion of cortisol. Given the closely associated steroidogenic pathways in the adrenals and the ovaries, it is unsurprising that both of these conditions share clinical features with PCOS. The former presents with central obesity, amenorrhea, high blood pressure and hirsutism, while the latter is characterised by androgen excess, menstrual irregularity and hirsutism. An elevated 24-hour cortisol test denotes Cushing's syndrome and refutes the PCOS diagnosis, in which the test is normal. The presence of CAH is confirmed when the circulating levels of 17-hydroxyprogesterone are greater than 500 ng/dL. Any value below 200 ng/dL excludes this diagnosis. Hyperprolactinemia, which shares the feature of galactorrhoea with PCOS, is considered more likely when the measured prolactin level is greater than 200 μg/L (65). In adolescent and adult females with CAH the question of the contribution of the *CYP21A2* heterozygosity to the pathogenesis of PCOS has recently been considered by several groups including ours. In a similar fashion all groups reported an increased frequency of *CYP21A2* heterozygosity in girls, female adolescents and women with clinical symptoms of androgen excess and PCOS (66-71). Markedly, also in our female cohort of heterozygous females we saw that those with the higher ACTH stimulated 17-OHP mean values belonged in the group of carriers with the c.1683G >T (p.Val281Leu) mutation (66, 68). This finding supports the already identified notion that carriers of the mild c.1683G >T (p.Val281Leu) missense mutation exhibit higher ACTH-stimulated 17-OHP values and higher rates of either PCOS (72).

Therapeutic management

Having established the multifactorial and complex nature of PCOS, management options involve a wide spectrum of both conservative and interventional treatments. These treatment options are largely targeting the signs and symptoms associated with the dysregulation of the reproductive system. Some of these management suggestions target the metabolic conditions, which are closely linked to the pathogenesis of PCOS and could prove highly detrimental to patients in the future. The initial approach to management requires the implementation of lifestyle modifications, after the failure of which pharmacological options are considered. In turn, the third-degree treatment involves interventional procedures (73).

Lifestyle modifications

The coexistence of high Body Mass Index (BMI >30kg/m^2) with PCOS was reported to be as high as 80%, something which is greatly attributable to the androgen excess, insulin resistance and subsequent hyperinsulinaemia observed in this syndrome. Lifestyle modifications, including dietary alterations and physical activity, were demonstrated to promote weight loss and thus enhance insulin sensitivity (32). This is supported by evidence published by Goss *et al.* who conducted a crossover study including 30 women with PCOS. The participants undertook a reduced-carbohydrate (CHO) diet for the first 8 weeks of the experiment and reverted back to their normal diet for the following 8 weeks. This intervention supported the effectiveness of dietary modifications in improving the metabolic syndrome associated with PCOS, as participants reported 3.7% loss of body fat, which was accompanied by raised insulin sensitivity (74). Low glycaemic index (GI) diet was also shown to be beneficial in the management of PCOS, as a study assessing its effectiveness reported that 95% of participants receiving this diet depicted improvement in the consistency of menstrual patterns. This effect in combination with an increase in insulin sensitivity supported the utilisation of a low GI diet in modulating the severity of the syndrome (75). The amount of saturated fats consumed should also be limited as it was exemplified that excessive amounts of trans fats negatively affect fertility and enhance insulin resistance (76). Further evidence suggests the introduction of regular physical activity in the daily routine of PCOS patients in an attempt to improve the associated symptoms. A study investigating the effect of regular exercise in PCOS patients, depicted that 60% of the women in the intervention group demonstrated improvements in the regularity of periods (77).

Oligo-anovulation and infertility

Pharmacological treatment

Clomiphene Citrate

The first-line pharmacological treatment for anovulation and infertility is clomiphene citrate (CC), whose role is to promote follicular maturation and ovulation. This drug binds on the oestrogen receptors and acts antagonistically to reduce the body's responsiveness to oestrogen. As a result, the negative feedback mechanism stimulates the release of GnRH, which would consequently promote the secretion of LH and FSH (78). Therefore, follicular maturation and ovulation is enhanced, and infertility as well as irregular menstruation are reduced. This is supported by a study investigating its efficacy, in which 80% of patients receiving CC experienced ovulation, while 40% were able to conceive a child. However, 20% of participants were proven resistant to the drug (79).

Gonadotropin therapy

In case when CC fails to provide the desired outcomes, gonadotropin therapy is offered as a second-line pharmacological intervention. The drug consists of a form of recombinant FSH or urinary-derived gonadotropins. When administered, the FSH aims to promote follicular proliferation and maturation, which would subsequently stimulate ovulation. It was previously reported that this form of treatment was 41% successful in achieving pregnancies in patients with PCOS (80).

Aromatase inhibitors

If the gonadotropin therapy fails to address the issue of infertility, aromatase inhibitors form the third-line pharmacological treatment option. Aromatase enzymes facilitate the production of oestrogen from testosterone in the ovaries, and thus inhibitory drugs, such as letrozole, diminish oestorgen secretion (81). The negative feedback pathway, consequently, stimulates FSH release, which in turn mediates follicular maturation and ovulation. When compared with CC, letrozole demonstrated as much as 25% higher pregnancy rates in PCOS patients (82).

Surgical intervention

When pharmacological treatment is insufficient for the management of anovulation and infertility, surgical intervention is attempted. The preferred approach is laparoscopic ovarian drilling, a procedure aiming to remove the tissue generating the excess androgens using electrosurgery or a laser. Electrosurgery is directed to the follicles located on the ovarian surface and the surgeon makes 4-20 puncture holes, which typically measure 3 by 3 mm on both ovaries. The lower postoperative pain, faster recovery, and improved cosmetic outcomes, associated with the minimally invasive approach, deem this procedure the ideal surgical intervention (83). A study investigating the effectiveness of this approach depicts promising results, as 76% of women receiving ovarian drilling experienced ovulation, while 81% conceived a baby (84).

In-vitro fertilisation (IVF)

When all of these treatment options prove fruitless, IVF is recommended to women who desire to have a baby. This process involves the extraction of female ova and male sperms, which in turn are artificially fertilised under laboratory conditions. The fertilised ovum is then implanted in the patient's uterus.

Menstrual irregularity

Irregular menses can be managed pharmacologically in women who do not desire to have a baby. The first-line management is the combined oral contraceptive pill (OCP) or the progesterone-only pill, both of which are used to regulate the disrupted hormonal patterns. This is only usually taken for the convenience of the woman as it can regulate their periods. If regular periods are not desired, then it is advised not to be taken (5).

An alternative to the OCP is metformin, which is the primary pharmacological treatment to type 2 diabetes and is classified as an antihyperglycaemic drug. This agent inhibits gluconeogenesis in the liver and reduces the circulating insulin. This in turn, reduces androgen production, and promotes follicular maturation and thus menstruation (85). However, metformin's efficacy is considered inferior to CC and letrozole (86).

Hirsutism

Hirsutism can be treated using a combined therapy of androgen reduction, peripheral androgen inhibition as well as cosmetic removal of excess hair. The preferred agent to diminish circulating androgens is the OCP, which reduces the LH excess observed in PCOS. An alternative includes the long-acting GnRH agonists, the excess of which suppresses androgens by reducing LH and FSH. Lifestyle modifications, including weight loss and physical activity in combination with agents, such as metformin, target insulin resistance, and thus, androgen production. Agents, such as spironolactone, flutamide, and cyproterone, hinder androgen activity at the receptor level and improve hirsutism. Lastly, patients can refer to cosmetic solutions, with which excess hair is sometimes adequately removed (81).

Conclusions

In summary, given the large prevalence of PCOS in women of child-bearing age, it is important to address the underlying mechanisms involved in its pathogenesis. The complex interaction of genetic, epigenetic, endocrine and environmental factors complicates the understanding of the aetiology of this syndrome, which is reflected in the variable phenotypes observed in patients with PCOS. This is also supported by the existence of multiple diagnostic guidelines which derive due to the conflict of expert opinions in defining the condition. Current treatment aims to address the reproductive dysregulation and the metabolic imbalance, and is therefore symptomatic in nature. Future research should focus on further describing the aetiological factors contributing to the development of PCOS in order to identify potential risk factors. Once recognised, preventative interventions can reduce the severity of the PCOS phenotype.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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Correspondence:
Nicos Skordis, MD, PhD
Paedi Center for Specialised Pediatrics
178, Athalassas avenue CY 2025 Nicosia, Cyprus
E-mail: nicosskordis@paedi.org.cy