

Polycystic ovary syndrome: a dermatologic approach

Síndrome do ovário poliquístico: uma abordagem dermatológica

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in women of reproductive age. It is a multifactorial disease with endocrinological, genetic, and environmental factors playing a role in its pathophysiology. The main diagnostic criteria include the presence of hyperandrogenism, chronic anovulation, and polycystic ovaries on ultrasound. Women with PCOS present a variety of signs and symptoms, as well as an increased risk of metabolic, cardiovascular, and reproductive disorders. This syndrome has an important psychological impact, and it is associated with a decreased quality of life. The dermatological manifestations, due to hyperandrogenism, include hirsutism, acne, and androgenetic alopecia. These manifestations provide clues for PCOS diagnosis, and early treatment is essential to improve the quality of life and well-being of patients. Thus, as part of a multidisciplinary approach, dermatologists play an essential role in the diagnosis and treatment of women with PCOS. Treatment includes hormonal therapy to control hyperandrogenism and non-hormonal therapy for each dermatological manifestation.

Keywords: Acne. Androgenetic alopecia. Hyperandrogenism. Hirsutism. Polycystic ovary syndrome.

Resumo

A síndrome do ovário poliquístico (SOP) é uma das endocrinopatias mais comuns na mulher em idade fértil. É uma doença multifatorial com fatores endocrinológicos, genéticos e ambientais a desempenharem um papel na sua fisiopatologia. Os principais critérios de diagnóstico incluem a presença de hiperandrogenismo, anovulação crónica e ovários poliquísticos em ecografia. As mulheres com SOP apresentam uma variedade de sinais e sintomas, assim como um aumento do risco metabólico, cardiovascular e reprodutivo, com impacto psicológico e diminuição da qualidade de vida. As principais manifestações dermatológicas, consequência do hiperandrogenismo, incluem o hirsutismo, a acne e a alopecia androgenética. Estas manifestações fornecem pistas para o diagnóstico da SOP e o tratamento precoce é importante na melhoria da qualidade de vida e do bem-estar das doentes. Assim, como parte de uma abordagem multidisciplinar, os dermatologistas representam um papel essencial no diagnóstico e orientação terapêutica de mulheres com SOP. A abordagem terapêutica inclui o tratamento hormonal para controlo do hiperandrogenismo e tratamento não hormonal direcionado a cada manifestação dermatológica.

Palavras-chave: Acne. Alopecia androgenética. Hiperandrogenismo. Hirsutismo. Síndrome do ovário poliquístico.

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Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in women of reproductive age, affecting 5-20% of women worldwide¹. This is a heterogeneous disease with a significant impact on a woman's quality of life, often associated with metabolic, cardiovascular, and obstetric complications². Although the diagnosis and early treatment are crucial for the quality of life and well-being of women with PCOS, most of them describe a delay in diagnosis, with multiple medical visits and inadequate health information until the definitive diagnosis³⁻⁵. In recent years, there has been an evolution in the classification criteria for this syndrome⁶. The first diagnostic criteria were proposed in 1990 by the National Institutes of Health (NIH)⁷, followed by the Rotterdam criteria proposed by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM)^{8,9}. In 2006, diagnostic criteria were proposed by the Androgen Excess Society (AES)^{10,11}.

PCOS can present with signs and symptoms associated with hyperandrogenism, menstrual irregularities, or polycystic ovaries on ultrasound¹². Cutaneous manifestations such as hirsutism, acne, and androgenetic alopecia (AGA) are among the earliest manifestations of this syndrome, providing a clue for its diagnosis¹³. Therefore, as part of a multidisciplinary approach, dermatologists play an essential role in the early diagnosis and treatment of women with PCOS.

This review aims to evaluate the current knowledge on PCOS, highlighting the diagnostic criteria, dermatological manifestations, and therapeutic guidelines for managing this syndrome, considering that most of these women require long-term treatment and follow-up.

Epidemiology

PCOS is recognized as one of the most common endocrine disorders in women. Its prevalence depends, in part, on the diagnostic criteria used to define this condition, considering that each criterion includes a variable number of PCOS phenotypes.

In a 2018 systematic review and meta-analysis, Skiba et al. analyzed the prevalence of PCOS according to the NIH, EHSRE/ASRM, and AES classifications, and the overall prevalence of PCOS was 7%, 12%, and 10%, respectively¹⁴. A 2022 systematic review and meta-analysis described prevalence rates

of 6%, 20%, and 15%, according to the NIH, EHSRE/ASRM, and AES criteria, respectively¹. The differences reported by the two studies are partly due to the geographical areas included. In the most recent review, only studies in Europe or America were included, where similar prevalence rates were reported between the two continents¹. Regarding PCOS in adolescence, prevalences of 3%, 11%, and 8% have been reported, according to the NIH, ESHRE/ASRM, and AES criteria, respectively¹⁵.

Pathophysiology

PCOS is a multifactorial disease with endocrinological, genetic, and environmental factors playing a role in its pathophysiology.

Regarding hormonal factors, this syndrome is characterized by hypothalamic-pituitary axis dysfunction and insulin resistance. Women with PCOS show an increased frequency of gonadotropin-releasing hormone pulses, resulting in preferential secretion of luteinizing hormone (LH). The relative increase in LH compared to follicle-stimulating hormone stimulates the production of androgens in the ovaries^{16,17}. In addition, there is a decrease in insulin sensitivity, with consequent hyperinsulinemia¹⁸⁻²⁰. In the ovaries, insulin stimulates the production of androgens by theca cells^{21,22} and, in the liver, inhibits the production of sex hormone-binding globulin (SHBG), increasing the bioavailability of androgens²³. Therefore, the presence of these two factors contributes to the characteristic hyperandrogenism of this syndrome (Fig. 1).

Obesity seems to contribute to the pathophysiological mechanism of PCOS due to its relationship with insulin resistance and consequent stimulation of androgen production, which contributes to the worsening of clinical manifestations of this syndrome²⁴ (Fig. 1).

The interaction between genetic and environmental factors also plays a role in the pathophysiology of PCOS. Several studies among family members of women with PCOS have demonstrated the hereditary component associated with this syndrome, with an association of 70% among monozygotic twins²⁵ and 20-40% among first-degree relatives^{26,27}. However, PCOS is currently considered a polygenic disease, resulting from the interaction of multiple genetic and environmental factors. Several genes have been described in association with the action of gonadotropins and insulin, energy regulation, steroidogenesis, and folliculogenesis^{28,29}.

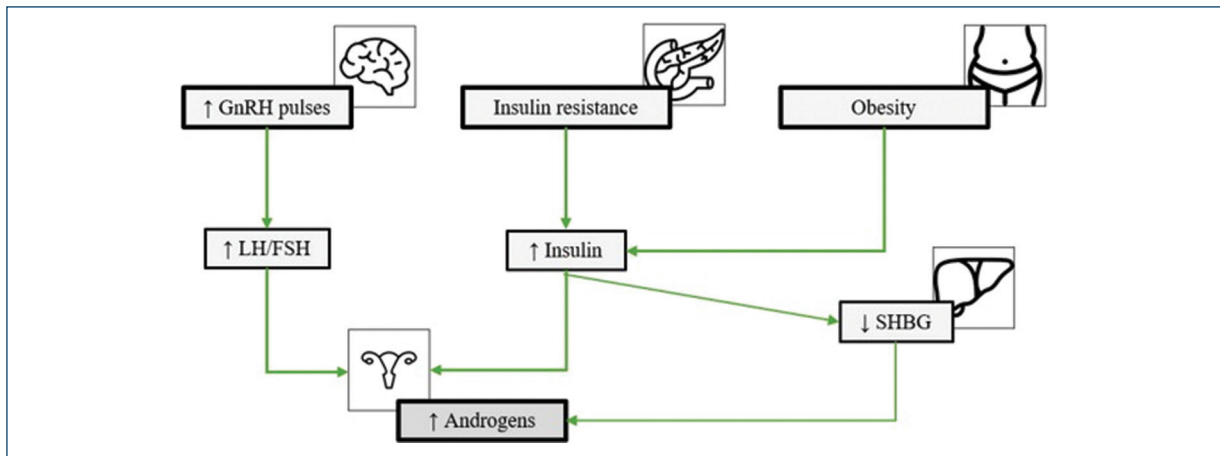


Figure 1. Pathophysiology of polycystic ovary syndrome. FSH: follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; LH: luteinizing hormone; SHBG: sex hormone binding globulin.

Diagnosis

Diagnostic criteria

PCOS is a widely recognized condition, first described in 1935³⁰. However, due to its complexity, several diagnostic criteria have been proposed over the past three decades (Table 1). In 1990, the first diagnostic criteria defined by the NIH included the presence of chronic oligo-anovulation and hyperandrogenism⁷. In 2003, at a consensus held in Rotterdam, ESHRE and ASRM proposed the addition of a new criterion: the presence of polycystic ovaries on ultrasound. According to this classification, the diagnosis of PCOS requires the presence of two of the following criteria: clinical or biochemical hyperandrogenism, chronic ovulatory dysfunction, and polycystic ovaries on ultrasound^{8,9}. In 2006, the EAS suggested a new definition of PCOS that included the presence of hyperandrogenism associated with ovarian dysfunction, such as the presence of oligo-anovulation or polycystic ovaries on ultrasound^{10,11}. Due to controversies between the different diagnostic criteria, in 2012, the NIH consensus proposed maintaining the Rotterdam criteria (ESHRE/ASRM), with the identification of four phenotypes: phenotype A with the presence of all three criteria; phenotype B with the presence of hyperandrogenism and ovulatory dysfunction; phenotype C with the presence of hyperandrogenism and polycystic ovaries; and phenotype D with ovulatory dysfunction and polycystic ovaries^{31,32}.

Finally, the 2023 international recommendations for the management of PCOS endorse the Rotterdam criteria (ESHRE/ASRM), with a particularity:

in the presence of menstrual irregularities and clinical and/or laboratory hyperandrogenism, ultrasound is unnecessary for the diagnosis¹².

Diagnostic approach

If a teenager or woman presents with clinical manifestations of hyperandrogenism, such as hirsutism, acne or AGA, and menstrual irregularities, the diagnosis of PCOS can be assumed (Fig. 2). However, in the isolated presence of menstrual irregularities, it is advisable to request laboratory studies assessing plasma androgen levels, measuring free and total testosterone¹². Androstenedione and dehydroepiandrosterone sulfate could be considered if total or free testosterone is not elevated, due to lower specificity of these hormone levels^{12,33,34}. In women taking combined oral contraceptives (COC), this should be discontinued within 3 months due to its suppressive effect on gonadotropins and ovarian androgens¹².

Ultrasound is only indicated for adult women with menstrual irregularities or hyperandrogenism. The diagnostic criteria for PCOS include the presence of ≥ 20 follicles in each ovary, ovarian volume > 10 mL, or ≥ 10 follicles per ovarian section¹² (Fig. 2).

Regardless of classification criteria, diagnosing PCOS involves excluding other pathologies or etiologies that may mimic it. Therefore, the presence of hyperprolactinemia, thyroid pathology, or non-classical congenital adrenal hyperplasia should be ruled out. Therefore, all women should be screened with thyroid-stimulating hormone,

Table 1. Diagnostic criteria for polycystic ovary syndrome

Classification	NIH 1990	ESHRE/ASRM 2003	AES 2006	NIH ESHRE/ASRM 2012
Criteria				
Hyperandrogenism (HA)	✓	✓	✓	✓
Chronic anovulation (CA)	✓	✓	✓	✓
Polycystic ovaries (PCO)	-	✓	-	✓
Number of criteria	2/2	2/3	2/2	2/3
Phenotype	-	-	-	A: HA + CA + PCO B: HA + CA C: HA + PCO D: CA + PCO

AES: Androgen Excess Society; ASRM: American Society for Reproductive Medicine; ESHRE: European Society of Human Reproduction and Embryology; NIH: National Institutes of Health.

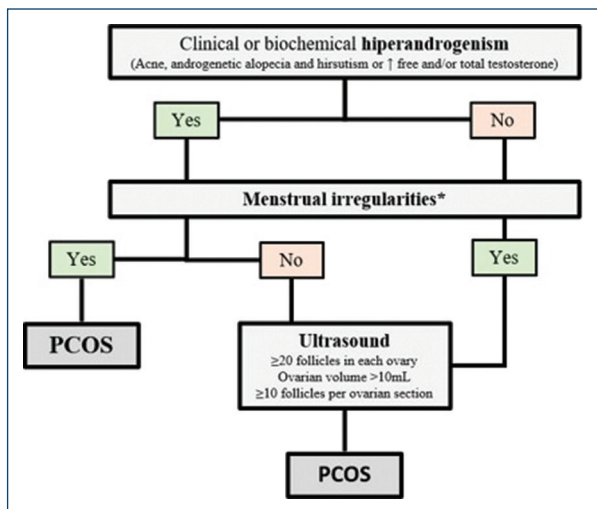


Figure 2. Diagnostic algorithm of polycystic ovary syndrome. PCOS: polycystic ovary syndrome.
*Irregular menstrual cycles: normal in the 1st year after menarche; < 21 days or > 45 days if 1-3 years after menarche; < 21 days or > 35 days or < 8 cycles per year if 3 years after menarche; > 90 days for any cycle.

prolactin, and 17-hydroxyprogesterone (Table 2). In the presence of other symptoms and according to clinical suspicion, other diagnoses should be considered, such as hypogonadotropic hypogonadism, Cushing's syndrome, or androgen-producing tumours^{12,34-36} (Table 3).

Dermatologic manifestations

Dermatological manifestations of PCOS are a consequence of excess circulating androgens and may include hirsutism (Fig. 3), acne (Fig. 3), and³⁷ (Fig. 4).

Hirsutism

Hirsutism is defined as excessive terminal hair growth in androgen-dependent areas in females and is one of the main manifestations associated with hyperandrogenism^{37,38}.

The prevalence of hirsutism in women with PCOS varies between 47% and 90%, according to different studies^{13,39-42}. In the hair follicle, there is an increase in the activity of the enzyme 5- α reductase, responsible for transforming testosterone into dihydrotestosterone (DHT), which is also stimulated by hyperandrogenism, insulin-like growth factor, and insulin^{43,44}. Testosterone and DHT are involved in the hair cycle, transforming vellus hairs into terminal hairs in anatomical areas sensitive to androgens, such as the face, neck, or pubic area^{45,46}.

The modified Ferriman-Gallwey scale is the most widely used method for classifying hirsutism. This scale scores the presence of terminal hair in nine female body areas, assigning a score between 0 and 4 for each⁴⁷. A score ≥ 8 is indicative of hirsutism^{48,49} (Fig. 5).

Acne

Acne is a multifactorial disease of the pilosebaceous unit and its pathophysiology includes follicular hyperkeratinization, inflammation, proliferation of *Cutibacterium acnes*, and increased sebum production. Genetic and extrinsic factors such as diet, medications, and environmental factors can also play a role in acne pathogenesis⁵⁰. Androgens stimulate the growth of sebaceous glands, increase sebum production, and promote the shedding of follicular epithelial cells. These factors promote the formation of comedones, which, in association

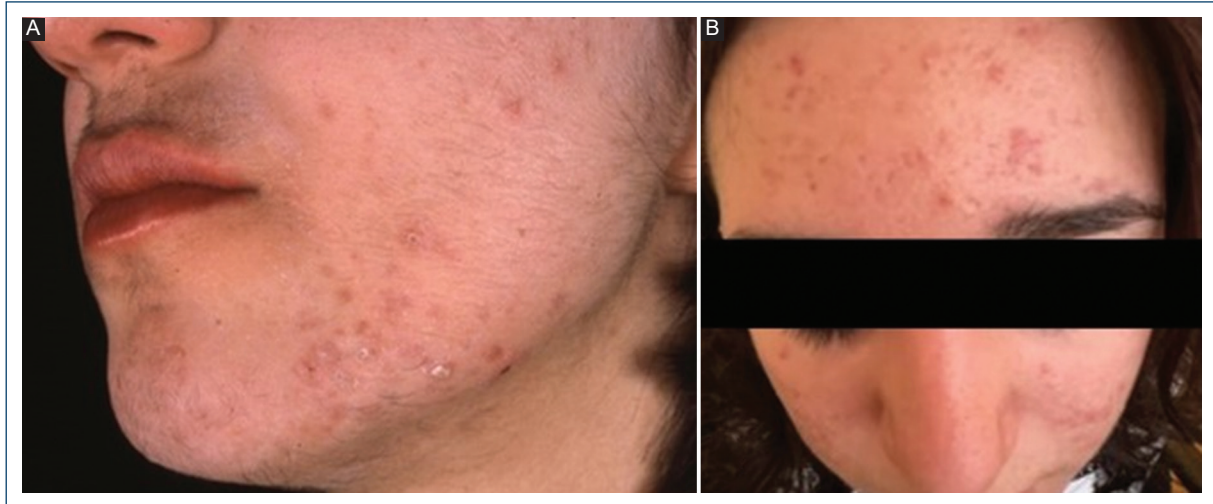


Figure 3. Women with hirsutism (A) and acne associated with polycystic ovary syndrome (B).



Figure 4. Androgenetic alopecia: Ludwig pattern (A) and Olsen pattern (B).

with colonization by *C. acnes*, trigger an inflammatory process, resulting in papules, pustules, nodules, or cysts^{43,51,52}. Acne is also a marker of hyperandrogenism, with prevalences of 40-75% in women with PCOS^{13,39-41}.

AGA

Female AGA is characterized by hair thinning in the central area of the scalp (Fig. 4A), due to the

miniaturization of terminal hair into vellus hair and the shortening of the anagen phase, influenced by androgens^{46,53}. This condition affects 20-43% of women with PCOS^{13,40,41}.

The Ludwig scale is one of the methods used to classify this alopecia and ranges from I to III, according to severity⁵⁴ (Fig. 6). Later on, the Olsen pattern was described, which is characterized by a marked hair thinning in the frontal hairline, known as the "Christmas tree" pattern⁵⁵ (Fig. 4B).

Table 2. Laboratory screening tests for polycystic ovary syndrome diagnosis

Blood tests for polycystic ovary syndrome
Free and/or total testosterone
Androstenedione*
Dehydroepiandrosterone sulfate*
Prolactin
Thyroid-stimulating hormone
17-hydroxyprogesterone

*Measuring androstenedione and dehydroepiandrosterone sulfate should be considered if testosterone or free testosterone is not elevated, according to the International Evidence-based Guideline¹².

Table 3. Differential diagnosis for polycystic ovary syndrome

Differential diagnosis	Laboratory studies
Thyroid disease	↑/↓ TSH – hyperthyroidism/ hypothyroidism
Hyperprolactinemia	↑ Prolactin
Non-classical congenital adrenal hyperplasia	↑ 17-hydroxyprogesterone
Cushing syndrome	↑ 24-h urinary cortisol ↑ Late-night salivary cortisol Negative dexamethasone suppression test
Adrenal tumors	↑ DHEA-S
Hypogonadotropic hypogonadism	↓ LH e FSH

DHEA-S: dehydroepiandrosterone sulfate; FSH: follicle-stimulating hormone; LH: luteinizing hormone; TSH: thyroid-stimulating hormone.

Other dermatologic manifestations

Other PCOS cutaneous manifestations include seborrhea and acanthosis nigricans, the latter associated with insulin resistance^{56,57}, with reported prevalences of 30-43% and 32-37%, respectively^{13,41}.

Complications

PCOS is associated with metabolic, cardiovascular, gynecological, and psychological complications^{2,58} (Table 4). Due to insulin resistance, women with PCOS have an increased risk of glucose intolerance, type 2 diabetes mellitus, and metabolic syndrome, as well as an increased cardiovascular risk due to its association with a high prevalence of hypertension, dyslipidemia, and obesity⁵⁹⁻⁶¹. Women with PCOS have a risk of up

to 7 times higher of developing type 2 diabetes mellitus and up to 3 times higher of metabolic syndrome^{62,63}.

Due to chronic anovulation, women with PCOS may have difficulty conceiving, with PCOS accounting for 80% of cases of anovulatory infertility⁶⁴. There is also an increased risk of endometrial hyperplasia and a 2-fold higher risk of endometrial carcinoma⁶⁵⁻⁶⁷.

Finally, the psychological consequences are associated with a negative impact on quality of life, with a higher prevalence of depression and anxiety in these women^{68,69}. Women with PCOS have a four times higher risk of developing depression and a 6 times higher risk of developing anxiety^{70,71}.

Therefore, the long-term health risks associated with PCOS highlight the relevance of early recognition of the syndrome, and dermatological manifestations may be among the earliest to be identified.

Treatment

Treatment of PCOS dermatological manifestations includes hormonal therapy aimed at reducing circulating androgen levels and inhibiting their action on target tissues (Table 5). In addition, there are various non-hormonal treatments for each manifestation that can be used as adjunctive or alternative therapies.

A healthy lifestyle is the treatment basis for this syndrome. There is evidence that diet, exercise, and weight loss are associated with an improvement in the clinical manifestations of the disease and a reduction in cardiovascular risk^{12,33,72}.

Hormonal treatment

COCs are recommended in women of reproductive age for treating manifestations associated with hyperandrogenism but also to treat menstrual irregularities¹². COC contains two active components: the estrogenic component and the progestative component⁷³. The estrogen component stimulates the production of SHBG, decreasing the bioavailability of androgens, with ethinylestradiol being the most used. Regarding the progestative component, its androgenic properties vary according to the progestin, with cyproterone acetate being the progestine with the greatest anti-androgenic activity^{74,75}. Other options may include COC containing a progestin with low affinity for the androgen receptor or a progestin with anti-androgen action, such as drospirenone, dienogest, desogestrel, gestodene, and chlormadinone acetate⁷⁶⁻⁷⁹. Guidelines do not

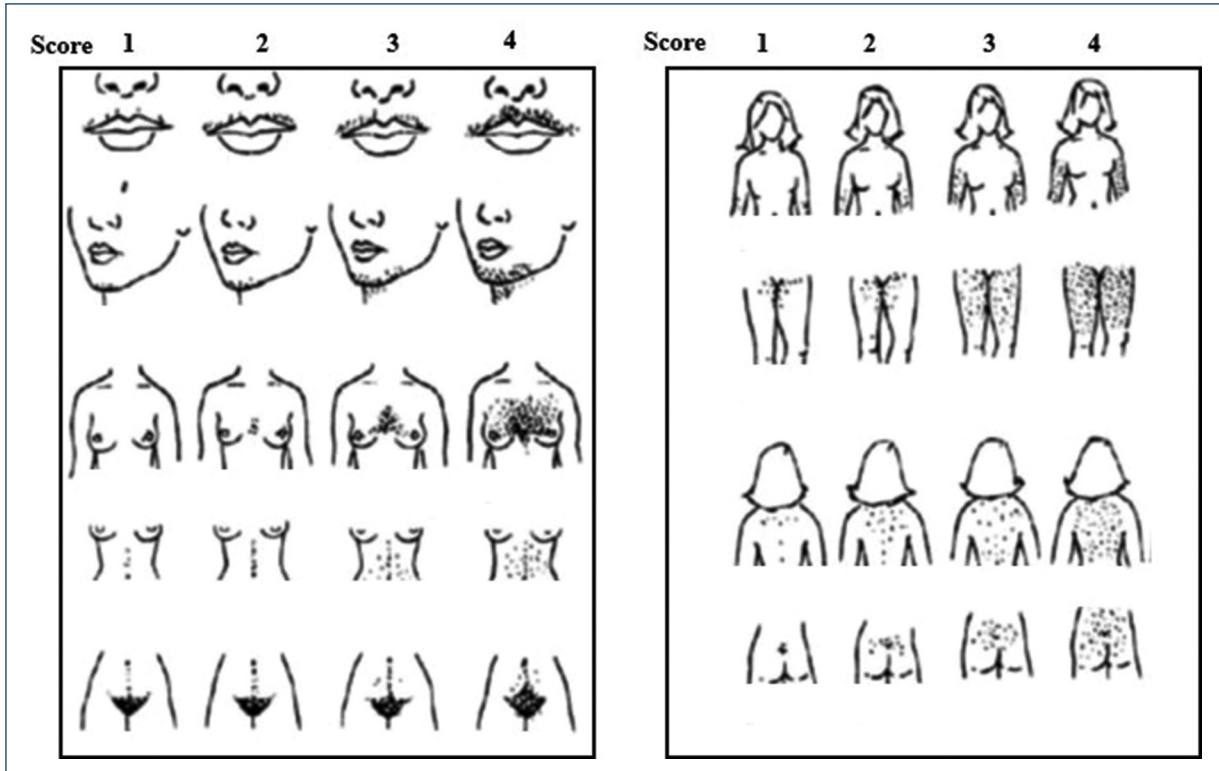


Figure 5. The modified Ferriman-Gallwey score for hirsutism. For each 9-body androgen-sensitive area, it is assigned a score of 0 (absence of terminal hair) to 4 (excess of terminal hair) (adapted from Hatch et al.³⁸).

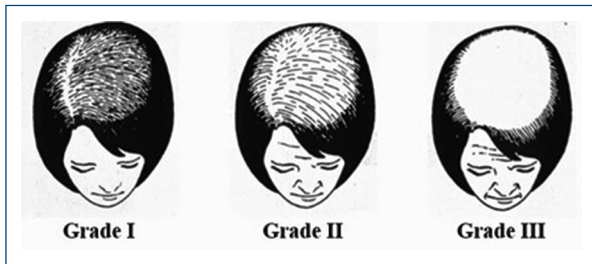


Figure 6. Ludwig scale for androgenetic alopecia (adapted from Ludwig⁵³).

Table 4. Non-dermatologic complications related to polycystic ovary syndrome

Complications	Disorders
Metabolic	Glucose intolerance Type 2 diabetes Metabolic syndrome Nonalcoholic fatty liver disease
Cardiovascular	Obesity Hypertension Dyslipidemia
Gynecological	Infertility Endometrial hyperplasia Endometrial carcinoma
Psychological	Anxiety Depression

suggest one formulation over another, due to the lack of clear evidence for differences in efficacy between preparations^{12,33,34}.

COC should be prescribed considering their efficacy, availability, metabolic risk, and adverse effects. There are many formulations of ethinylestradiol and both high and low doses are equally effective. The main adverse effect is the increased risk of venous thrombotic events⁷⁶.

Therefore, COC with a high dose of ethinylestradiol and cyproterone acetate are not recommended as first-line treatment in PCOS¹².

Antiandrogenic drugs should be considered when COC is contraindicated, poorly tolerated, or there is a suboptimal response after at least 6 months of treatment¹². These drugs act by inhibiting androgen

receptors, decreasing androgen production, or inhibiting the enzyme 5- α reductase. Its use requires effective contraception due to the risk of male fetus feminization if a pregnancy occurs⁸⁰. The most widely used anti-androgen drug is spironolactone, with good tolerance and a low adverse effect profile. Other options include finasteride, cyproterone acetate, bicalutamide, and flutamide, the latter two being less commonly used due to their hepatotoxicity^{12,81,82}. Dutasteride may be an option, especially indicated in AGA⁸². At least 6-12 months of antiandrogen therapy is required for clinical improvement⁸³.

Metformin is an insulin-sensitizing drug that inhibits gluconeogenesis and lipogenesis and prevents weight gain by acting in the appetite regulatory pathways⁸⁴. Metformin is recommended for metabolic indications in PCOS, while COC should be used for the management of hirsutism and irregular cycles¹². A recent meta-analysis revealed that the combined treatment with metformin and COC improved biochemical hyperandrogenism, insulin levels, and insulin resistance more than COC alone⁸⁴.

Non-hormonal treatment

HIRSUTISM

The management of hirsutism may include topical treatment or permanent hair removal techniques. Eflornithine hydrochloride is a topical drug that can be used as an adjuvant therapy due to its effect on inhibiting hair growth^{85,86}. Permanent hair removal techniques include electrolysis and photodepilation with intense pulsed light or laser. Multiple sessions with regular intervals are required to achieve results⁸⁷⁻⁸⁹.

ACNE

Acne treatments are alternatives or adjuncts to hormonal treatment and may include topical treatments (retinoids, benzoyl peroxide, antibiotics, salicylic acid or azelaic acid, either as monotherapy or in combination, except for topical antibiotics, which should not be used as monotherapy)⁹⁰ or oral therapy, namely antibiotics such as tetracyclines (doxycycline or minocycline) or isotretinoin, an oral retinoid that targets all four pathogenic factors of acne⁹⁰.

Table 5. Treatment options for polycystic ovary syndrome

Drug	Dose
Oral contraceptives Ethinylestradiol Cyproterone acetate Drospirenone Dienogest Desogestrel Gestodene Chlormadinone acetate	Variable doses
Antiandrogens Spironolactone Finasteride Dutasteride* Bicalutamide [†] Flutamide [†] Cyproterone acetate	25-200 mg/day 2.5-5 mg/day 0.15-0.5 mg/day 25-50 mg/day 250 mg/day Not recommended \geq 10 mg
Metformin	500-2000 mg/day

Antiandrogens could be used to treat hirsutism if at least 6 months of COC and cosmetic therapy have failed to adequately improve symptoms. Irrespective of the drug used, at least 6-12 months of antiandrogen therapy is required for clinical improvement.

*For androgenetic alopecia.

[†]Increased risk of hepatotoxicity.

AGA

AGA treatment includes topical or oral therapy. Topical minoxidil is the first-line treatment for women with AGA. Its therapeutic effect can be enhanced by oral drugs such as spironolactone, a drug with anti-androgenic potential, or finasteride, an inhibitor of the 5- α reductase enzyme^{91,92}. Dutasteride is a potential alternative to finasteride because it is more potent at inhibiting 5 alfa reductase⁹³. Other options include oral minoxidil or topical finasteride in combination with topical minoxidil. Other therapeutic modalities include platelet-rich plasma injection⁹⁴, low-level laser therapy⁹⁵, as well as hair transplantation if there is a poor response to pharmacological treatment^{93,96,97}.

Conclusion

PCOS is one of the most common endocrine disorders in women of reproductive age and is associated with several long-term risks with a significant psychological impact on adolescents and women. It is a multifactorial condition that requires a multidisciplinary approach. Dermatological manifestations such as hirsutism, acne, or AGA play a key role in its diagnosis, and the dermatologist is crucial in its management and treatment. Hormonal treatment aims to minimize the effect of androgens on the skin and hair follicles.

Several non-hormonal treatments can be used as adjunctive or alternative therapy.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript or for the creation of images, graphics, tables, or their corresponding captions.

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