

Polycystic ovary syndrome: a dermatologic approach ^{*}

Síndrome do ovário policístico: abordagem dermatológica

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Abstract: Polycystic ovary syndrome (POS) is one of the most common endocrine abnormalities affecting women of reproductive age. It is a cause of significant social embarrassment and emotional distress. The pathogenesis of the disease is not yet fully understood, but it is thought to be a complex multigenic disorder, including abnormalities in the hypothalamic-pituitary axis, steroidogenesis, and insulin resistance. The main diagnostic findings of the syndrome are: hyperandrogenism, chronic anovulation and polycystic ovarian morphology seen on ultrasound. Hyperandrogenism is generally manifested as hirsutism, acne, seborrhea, androgenic alopecia and, in severe cases, signs of virilization. Treatment may improve the clinical manifestations of excess androgen production, normalize menses and ameliorate metabolic syndrome and cardiovascular complications. This article reviews the diagnosis, clinical manifestations, metabolic complications, and treatment of the syndrome. Early diagnosis and the consequent early treatment may prevent metabolic complications and emotional distress that negatively impact the patients' quality of life.

Keywords: Acanthosis nigricans; Acne vulgaris; Alopecia; Hyperandrogenism; Polycystic ovary syndrome

Resumo: A síndrome do ovário policístico (SOP) é uma das endocrinopatias mais frequentes nas mulheres em idade reprodutiva. Caracteriza-se por morbidade elevada devido aos aspectos estéticos e por repercussões metabólicas importantes. Embora a sua patogênese permaneça incompletamente conhecida, acredita-se numa desordem multigênica complexa, incluindo anormalidades no eixo hipotálamo-hipofisário, esteroidogênese e resistência insulínica. Os achados principais para o diagnóstico são: hiperandrogenismo, anovulação crônica e ovários policísticos à ultrassonografia. As manifestações dermatológicas do hiperandrogenismo incluem: hirsutismo, acne, seborréia, alopecia e, em casos mais graves, sinais de virilização. Existe considerável heterogeneidade nos achados clínicos e também pode haver variação na mesma paciente com o passar do tempo. O tratamento visa reduzir as manifestações do hiperandrogenismo, restaurar os ciclos ovulatórios regulares e corrigir a síndrome metabólica. Este artigo apresenta revisão da fisiopatologia, diagnóstico e tratamento da síndrome do ovário policístico. Enfatiza-se a importância do diagnóstico e tratamento precoces no intuito de prevenir as complicações metabólicas e a repercussão emocional que afeta a qualidade de vida das pacientes.

Palavras-chave: Acantose nigricans; Acne vulgar; Alopecia; Hiperandrogenismo; Síndrome do ovário policístico

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INTRODUCTION

Polycystic ovary syndrome (PCOS), originally described in the 1930s by Stein and Leventhal, is one of the most common endocrinopathies in women of reproductive age.¹ It is often characterized by hyperandrogenism, which may often be manifested as: hirsutism, acne, seborrhea, alopecia, menstrual irregularity, obesity and ovarian cysts. PCOS shows reproductive and metabolic complications that must be diagnosed and treated early due to the risk of infertility, endometrial cancer and plurimetabolic syndrome. Besides these complications, PCOS is associated with high morbidity due to aesthetic aspects that negatively affect women's self-esteem. Knowledge about the physiopathologic mechanisms of this syndrome is very important for an appropriate therapeutic approach.

CLASSIFICATION AND EPIDEMIOLOGY

The key findings for the diagnosis of PCOS are: hyperandrogenism, chronic anovulation and polycystic ovaries on ultrasound. However, other conditions may present with these manifestations, making differential diagnosis necessary.

Only a third of the patients have the classical form of the syndrome described by Stein and Leventhal, defined by the presence of amenorrhea, hirsutism and bilateral enlargement of the ovaries. Therefore, in 1990, the conference of the *National Institutes of Health (NIH)* suggested new diagnostic criteria represented by clinical and/or biochemical evidence of hyperandrogenism associated with oligoamenorrhea, with the exclusion of other causes of hyperandrogenism. In 2003, a new consensus was established by the *European Society for Human Reproduction and Embryology* and the *American Society for Reproductive Medicine* in Rotterdam - The Netherlands, which defined the syndrome as the presence of two or more manifestations that included, besides those defined by the *NIH*, the

presence of polycystic ovaries on ultrasound.² In 2006, the *Androgen Excess Society* gave emphasis to hyperandrogenism, suggesting that this would be a mandatory criterion for the diagnosis of the syndrome (Chart 1).³

PCOS affects women of childbearing age, with no predilection for race, but the signs and symptoms may differ in various ethnic groups. Prevalence varies from 4-10%, depending on the diagnostic criteria used.^{4,5} By the Rotterdam criteria, the prevalence is five times higher than that defined by the criteria of the *NIH*.⁶

PATHOGENESIS

The etiology of PCOS is not yet fully understood. It is believed that there is multigenic complex disorder, including abnormalities in the hypothalamic-pituitary axis, steroidogenesis and insulin resistance.⁷

Abnormal steroidogenesis

Most authors consider that abnormal steroidogenesis, of ovarian or adrenal origin, is the primary disorder of PCOS. High concentrations of circulating testosterone and dehydroepiandrosterone (DHEA) occur in 60-80% and 20-25% of women with PCOS, respectively.^{6,8} There is also an increase in estradiol production by ovarian granulosa cells associated with excess androgen levels. (Chart 2).⁹

Insulin resistance

Over the last decade, it has been observed that most women with PCOS have some degree of insulin resistance, even non-obese ones. Studies suggest the existence of genetic predisposition, which ends up manifesting as a result of lifestyle and obesity.

Hyperinsulinemia resulting from insulin resistance leads to an increase in the production of androgens and also in their biologically active

CHART 1: Diagnostic criteria for PCOS

National Institutes of Health (NIH) – 1990	1. Clinical and / or biochemical evidence of hyperandrogenism * 2. Oligoamenorrhea
European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine - 2003	1. Clinical and / or biochemical evidence of hyperandrogenism * 2. Oligoamenorrhea 3. Polycystic ovaries on ultrasound
Androgen Excess Society - 2006	1. Clinical and / or biochemical evidence of hyperandrogenism † 2. Oligoamenorrhea 3. Polycystic ovaries on ultrasound

* Other causes of hyperandrogenism should be excluded

† Essential for diagnosis

CHART 2: Effects of abnormal steroidogenesis

Increase of testosterone and DHEA	Interferes with the maturation of follicles and the emergence of the dominant follicle Reduces hepatic SHBG production
Increase of estradiol	Increased risk of endometrial and breast cancer

DHEA: Dehydroepiandrosterone
SHBG: sex hormone binding globulin

portion. The common suggested mechanism for this is associated with changes in insulin receptors and in the enzyme that regulates the production of adrenal and ovarian androgens.¹⁰ The systemic effects of hyperinsulinemia are described in chart 3.^{11, 12}

Abnormalities in pituitary function:

An imbalance in the release of the luteinizing hormone (LH) and the follicle stimulating hormone (FSH) from the pituitary has been implicated in the pathogenesis of PCOS. In patients with PCOS, the LH / FSH ratio is altered and the secretion of LH is higher than that of FSH, resulting in increased androgen production by theca cells and in anovulatory cycles.¹²
¹³ However, recent studies have shown that changes in LH levels are a secondary and not primary event.¹³

Thus, higher levels of circulating androstenedione are observed, with a consequent increase in the peripheral conversion of this hormone into testosterone. Excess androgen levels alter the regulation of female hormones, resulting in increased estrogen levels, menstrual irregularities and infertility.^{6, 7, 12}

CLINICAL MANIFESTATIONS

The clinical dermatologic manifestations of hyperandrogenism include: hirsutism, acne, seborrhea, alopecia, and in severe cases, signs of virilization. There is considerable heterogeneity in clinical findings, as there may be variation in the same patient over time. For instance, hyperandrogenism may not determine peripheral manifestations, as seen mainly in Asian women.

CHART 3: Effects of Hyperinsulinemia

Accelerates lipogenesis ? Increases production of free fatty acids;
Reduced levels of SHBG;
Increased LH and FSH levels

SHBG: sex hormone binding globulin
LH: Luteinizing Hormone
FSH: Follicle Stimulating Hormone

Hirsutism

Hirsutism is defined as excessive growth of terminal hair in androgen-dependent areas in women. It is one of the most commonly used clinical criteria for the diagnosis of excess androgen levels, being observed in 50-80% of the patients with hyperandrogenism.¹⁴⁻¹⁶

The Ferriman-Gallwey scale is used for the diagnosis of hirsutism. The disorder is considered present when the score is ≥ 8. However, this score is examiner-dependent and does not consider the impact of hirsutism on the well being of the patient.¹⁵⁻¹⁸ There is no correlation of the score with androgen levels, since the response of the pilosebaceous unit to androgens varies considerably (Figure 1).^{17, 19, 20}

The formation of hair follicles occurs during fetal development, and their concentration reflects ethnic differences. The speed of hair growth varies according to genetic differences in the activity of the enzyme 5α-reductase, which converts testosterone into dihydrotestosterone (DHT), which is the most potent metabolite. There are two isoenzymes of 5α-reductase: type 1, present in the sebaceous glands and skin of the pubic region, and type 2, found in hair follicles, scalp and genital area. Differences in the activity of the two enzymes determine the variation of clinical presentations in women with hyperandrogenism. It is established that hirsute women have increased activity of 5α-reductase in the hair follicles. The activity of 5α-reductase is stimulated by hyperandrogenism, insulin-like growth factor (IGF)

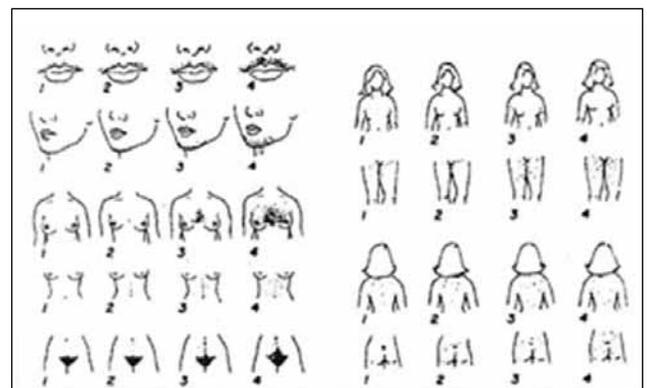


FIGURE 1: Ferriman-Gallwey Scale⁶

and by insulin itself.²¹

Testosterone and DHT determine alterations in the hair and in its cycle. They irreversibly transform *vellus* hair into terminal hair, thicker and more pigmented, in androgen-sensitive areas (face, neck, chest and pubic region), after months or years of exposure.^{16,17} The duration of the anagen phase is also related to levels of circulating androgens and varies in the different regions of the body. Androgens prolong the anagen phase in follicles of the body and shorten it in some areas of the scalp.¹⁶

To differentiate hirsutism from hypertrichosis in women, it is necessary to determine the type of excess hair and its distribution. Hypertrichosis is excessive hair in the entire body; the growth of *vellus* hair in androgen-independent areas, such as forearms and calves, is also considered a manifestation of the disease. Excess of *vellus* hair alone does not reflect hyperandrogenism, as the former may be associated with hereditary factors, medication, metabolic disorders or physical irritation of the skin.¹⁷ In hirsutism there is an increase of terminal hair in androgen-dependent areas.

Acne

Acne is a pilosebaceous unit disorder with lesions on the face, neck, back and pectoral region.

The importance of androgens in the pathogenesis of acne is well documented. However, since in acne vulgaris androgen levels are usually normal, it is believed that local conversion is enhanced by increased receptor sensitivity to androgens in acne patients as compared with the normal population, perhaps representing the most important triggering factor of the disease.^{15,22}

Androgens not only enlarge the sebaceous glands and increase sebum production, but also cause abnormal desquamation of follicular epithelial cells. These factors determine the formation of comedones and, in combination with the colonization of the follicle by *Propionibacterium acnes*, result in inflammation and progressive development of papules, pustules, nodules, cysts and scars.⁹

Several studies attempt to correlate the clinical presentation of acne with markers of hyperandrogenism. Although some authors have shown a correlation between acne and high levels of dehydroepiandrosterone sulfate (DHEA-S), DHT, androstenedione, testosterone and IGF, others did not corroborate this finding.^{15, 20-22}

Androgenetic Alopecia

Androgenetic alopecia in women is characterized by loss of hair in the central region of the scalp, with relevant psychosocial repercussions.

In the presence of androgen, high levels of 5-alpha reductase, higher concentration of androgen receptors and lower levels of the enzyme cytochrome p450, the anagen phase is shortened, and the terminal follicles undergo miniaturization, turning into *vellus* hair.^{16, 21} Changes may occur diffusely, but they are usually more evident in the frontal and parietal regions.

The diagnosis should exclude other causes of hair loss in women, such as telogen effluvium, alopecia areata, anagen loss syndrome and trichotillomania.¹⁵

Most patients with androgenetic alopecia have normal endocrine function. Thus, physical examination and medical history are important in the search for other signs of hyperandrogenism.²³ Additional tests may be needed, such as hair density, hematological and biochemical evaluations, and histological examination of the scalp to demonstrate miniaturized hair.

Acanthosis nigricans

Acanthosis nigricans is characterized by brown and velvety hyperpigmentation of the skin with accentuation on skin folds. It is most commonly observed in the neck and intertriginous areas, such as armpits, groins and inframammary region. It is reported in 5% of the patients with PCOS.⁹

Excessive binding of serum insulin to IGF-1 receptors in peripheral tissues determines the proliferation of keratinocytes and fibroblasts; hence, acanthosis nigricans is a cutaneous manifestation of hyperinsulinemia, and not just of obesity. Histologically there is papillomatosis, hyperkeratosis and acanthosis with minimal or no hyperpigmentation of the basal layer.

Despite being mostly associated with obesity, PCOS and diabetes, acanthosis nigricans may be associated with genetic diseases, drug reaction (nicotinic acid) and malignancies.¹⁵

The presence of acanthosis nigricans suggests the performance of the glucose tolerance test.²⁴ When severe, extensive and progressive, it may be associated with malignancy, especially if mucous membranes are also involved.¹⁵

Other Complications

The dysfunction of multiple hormone systems that characterize PCOS determines increased risk for many diseases.⁸ It is therefore important to evaluate and monitor patients to reduce morbidity and clinical implications.

Glucose intolerance and diabetes are considered the most important disorders in women with PCOS.^{6, 9, 25} There is no consensus, but it is

believed that PCOS is related to increased risk for cardiovascular disease.^{8, 26} However, clinical observations did not show greater morbidity and/or mortality in women with PCOS, despite the recognized association between insulin resistance and lipid profile changes.^{8, 9, 12}

Because PCOS is associated with irregular menstrual cycles, women may experience difficulty getting pregnant, endometrial hyperplasia and endometrial carcinoma.^{9, 12} These patients have a higher prevalence of abortion, ovarian and breast cancer, nonalcoholic steatohepatitis, obstructive sleep apnea and symptoms of depression.^{8, 9, 27}

Evaluation

The clinical diagnosis of PCOS is based on specific diagnostic criteria (Chart 4), but due to variable symptomatology, close attention to signs and symptoms is required.^{6, 10}

Clinical evaluation

The evaluation should include detailed menstrual history, information about the onset and duration of symptoms suggestive of hyperandrogenism and family history of PCOS and metabolic diseases^{8-10, 28}. Abrupt changes in the menstrual pattern or symptoms of hyperandrogenism should alert us to other etiologies²⁸.

The most frequent clinical manifestations include menstrual irregularity or amenorrhea, which can be masked by the use of oral contraceptives (OC). However, some women with PCOS have regular ovulatory cycles.

Examination of the genital region can be accomplished using the Tanner Scale, which analyzes the development of primary and secondary sexual characteristics and identifies signs of virilization. Clitoromegaly and voice changes are rare findings suggestive of adrenal tumors¹⁰.

Laboratory Evaluation

The main feature to confirm PCOS is the detection of excessive androgen levels through laboratory tests, although consensus allows only

clinical evidence of hyperandrogenism^{17, 29}. The recommendation of the Endocrine Society in 2008 for the evaluation of serum androgen levels in hirsute patients is listed below (Chart 5).

Among androgens, testosterone is the primary hormone in the evaluation of hirsutism and PCOS. However, most available methods are not very accurate, so their analysis should be cautious^{17, 29}. The most sensitive and precise methods are radioimmunoassays and tandem mass spectrometry.

Free testosterone is the most sensitive for the detection of hyperandrogenism^{10, 29}. This is because sex hormone-binding globulin (SHBG), which is the main determinant of the bioactive portion of plasma testosterone (free or bioavailable testosterone), is reduced in patients with hyperandrogenism. No tests are available for the direct measurement of this hormone. The best method is to calculate it by the product of total testosterone and SHBG function (e.g., free testosterone = total testosterone x percentage of free testosterone)^{29, 30}. These tests should be performed early in the morning, between the 4th-10th days of the menstrual cycle (women with regular cycles) or in women with amenorrhea. Patients with symptoms consistent of PCOS but without testosterone level changes must repeat the exam.

The dosage of other androgens in most cases is of little use. However, it is necessary to exclude other relatively common conditions that have specific treatment. The tests usually required and their main indications are listed in chart 6.

If the screening for disorders that most commonly mimic PCOS is negative, the association of high levels of testosterone and anovulatory symptoms meet the criteria for this syndrome. However, other rare disorders associated with androgen excess cannot be ruled out and an expert evaluation should be conducted to determine the source of androgen excess in these cases¹⁷.

CHART 4: Diagnostic Criteria for PCOS

Two of the three criteria below and exclusion of other etiologies (e.g., congenital hyperplasia, androgenic tumors, Cushing syndrome)

1. Oligo and / or anovulation
2. Clinical and / or biochemical signs of hyperandrogenism
3. Polycystic ovaries

CHART 5: Evidence for assessment of serum androgen levels

- Moderate to severe hirsutism (score > 15)
- Hirsutism (any grade) of sudden and progressive onset
- Hirsutism (any grade) associated with any of the fol

lowing findings:
 Menstrual irregularity or infertility;
 Central obesity;
 Acne, seborrhea, alopecia
 Acanthosis nigricans;
 Rapid progression;
 Clitoromegaly;

The LH / FSH ratio is no longer recommended for routine diagnosis of PCOS ². This is because there are differences between the data supplied by various tests (radioimmunoassay with polyclonal antibodies, monoclonal antibody radioimmunoassay, immunometric assays), body mass index of the patient and day of the cycle in which the test is done. Moreover, the relationship of the LH/FSH ratio in the pathogenesis of PCOS has not been confirmed. However, FSH is important in the diagnosis of primary ovarian failure, when FSH levels are high in relation to LH and estrogen ³¹.

Among other laboratory tests, it is important to remember the metabolic changes that may be related to PCOS, since they are associated with high morbidity. The glucose tolerance test should be requested of obese women and those at risk for type 2 diabetes, such as family history ¹⁰. Periodic assessment of lipid profile is recommended, as well as liver function monitoring when there are risk factors for hepatic steatosis (nonalcoholic fatty liver disease) ^{11, 32}.

Radiological Assessment

Indication of pelvic ultrasonography is still controversial. The classical presentation of PCOS is characterized by ovaries with a polycystic aspect, with more than eight subcortical cysts smaller than 10 mm and/or increased ovarian volume (> 10ml) ². The examination should be performed early in the follicular phase of the cycle (third to fifth day). In oligo / amenorrheic patients, the exam may be

performed randomly or after 3-5 days of bleeding induced by progestogens. However, 20% of the patients did not reveal changes on ultrasound ⁶. Moreover, many healthy women or those with other disorders related to excess androgens may have polycystic ovaries to the examination without presenting the other findings of the syndrome ²⁹.

TREATMENT

The treatment of PCOS seeks to reduce the signs of hyperandrogenism, restore regular ovulatory cycles and control features of the metabolic syndrome. The choice of treatment will depend on the severity of the symptoms and specific goals, always considering the possible long-term consequences.

Changes in lifestyle

It is the most effective and inexpensive approach, without adverse reactions. It consists in the practice of regular physical activity and in the adoption of a balanced diet. The loss of only 2-7% of weight improves almost all the parameters of PCOS by reducing androgen levels and improving ovarian function ¹⁰. These effects are related to the reduction in insulin levels and improvement of insulin resistance ³³.

Hormonal Treatment

The estrogen-progesterone combination therapy remains the main option for the treatment of hyperandrogenism for women who do not wish to become pregnant. It can be effective for hirsutism,

CHART 6: Assessment of disorders that most commonly mimic PCOS

Exam	Indication
Pregnancy Test	Amenorrhea
Prolactin Dosage	Irregular menstrual cycles, to exclude prolactinoma
DHEA Dosage	Cystic acne, suspicion of a virilizing tumor
17-hydroxyprogesterone dosage *	High risk of adrenal hyperplasia, such as positive family history and ethnic groups at high risk (Ashkenazi Jewish, Hispanic and Slavic women)
TSH	Irregular menstrual cycles, oligoamenorrhea
Dexamethasone suppression test / 24h urinary cortisol	Other findings, Cushing Syndrome
Dosage Somatomedin C / IGF-1	Other findings suggestive of acromegaly

* It should be performed early in the morning, in the follicular phase of the menstrual cycle

DHEA: Dehydroepiandrosterone
 TSH: thyroid-stimulating hormone
 IGF-1: Insulin Growth Factor-like type 1

acne and androgenic alopecia, and to prevent endometrial hyperplasia and its complications¹⁴.

Oral contraceptives (OC) are composed of ethinyl estradiol and a progestin. Estrogen suppresses the LH, decreasing androgen production by the ovaries and increasing the production of SHBG, reducing free testosterone^{17,33}.

Most progestins are derivatives of testosterone and have androgenic activity (Chart 7).

Drospirenone (DRSP) and cyproterone acetate (CPA) are not structurally related to testosterone and act as androgen receptor antagonists¹⁷. CPA also acts on androgen receptors, has little inhibitory effect on 5- α -reductase and reduces the secretion of androgen through anti-gonadotropin action^{17,34}. It may be used as monotherapy in some cases.

Drospirenone is a spironolactone analogue with equivalent effect to a dose of 25mg. It acts as anti-mineralocorticoid, but has a weaker anti-androgen action¹⁷.

The main OC used for the treatment of hirsutism contains CPA associated with estrogen.³³ Some studies confirm its efficacy, with a more rapid reduction in hair growth when compared with other anti-androgens. Similar efficacy has been observed with OC constituted by drospirenone¹⁷.

The use of OC should be maintained until reproductive maturity, approximately 5 years after menarche or until the ideal weight. The normalization of menstrual cycles and the improvement of acne and hirsutism occur, in general, three months after the start of the treatment. Some studies have shown that suppression of serum androgens remains for at least 2 years after discontinuation of OC, although most patients experience worsening three months after the end of treatment¹⁰.

Worsening of insulin resistance and increased levels of triglycerides and cholesterol associated with OC use have been reported³³. Other side effects include hypercoagulability, thrombogenic (mainly CPA) and vascular reactivity, demanding caution in patients with a history of vascular diseases such as migraine¹⁰.

Anti-androgenic drugs block the binding of androgens to their tissue receptors or inhibit the 5 α -reductase enzyme. All anti-androgens should be

prescribed in combination with oral contraceptives due to menstrual irregularities and risk of incomplete virilization of male embryo during pregnancy³⁵. In the treatment of hirsutism, they revert the transformation induced by androgens of *vellus* hair into terminal hair. Due to the long cycle of terminal hairs, the effect is only observed 9-12 months after the initiation of treatment¹⁰.

Spironolactone, an aldosterone antagonist, has dose-dependent action, blocking the binding of 5- α dihydrotestosterone to androgen receptors of the skin, increasing SHBG, reducing the activity of 5- α -reductase and androgen production. It is effective in treating hirsutism and it is believed that it could also improve acne and alopecia. It is generally well tolerated, although hypotension, polyuria, nausea, headache, fatigue and menstrual irregularity have been reported^{10, 17, 33}. The therapeutic regimen for hirsutism is 25 to 100mg twice daily and for acne, 100mg once daily¹⁵. The initial dose should be 25 mg / day and increased progressively over weeks¹⁰. Hyperkalemia has been reported only in women with renal dysfunction or in those taking other potassium-sparing medication.

Flutamide, a potent nonsteroidal anti-androgen, blocks the action of androgens by competitive inhibition of receptors, while reducing androgen synthesis or increasing its inactivation³⁵. The recommended dose is 250 to 750mg/day, but lower doses (62.5 to 250 mg daily) also appear to be effective. It is very effective in the treatment of hirsutism, acne and alopecia, but it has a high cost and risk of liver toxicity that is dose dependent and, although rare, potentially fatal¹⁷. The most common side effect is dry skin due to reduced production of sebum^{33,34}. Its use is not authorized in Brazil.

Finasteride, a type 2 inhibitor of 5 α -reductase, blocks the conversion of testosterone into DHT^{15,17}. Despite the fact that the pilosebaceous unit has predominantly type 1 enzyme, studies show a beneficial effect in the treatment of hirsutism, as well as that of androgenic alopecia in women, with few side effects¹⁰. However, it does not seem to be effective in treating acne. The dose used is 1 mg / day, although safety at higher doses has been described¹⁵.

Dutasteride acts on both isoenzymes 5 α -reductase and induces an even greater reduction in serum levels of DHT, with evidence of benefit in the treatment of female androgenic alopecia at a dose of 0.5 mg / day^{23,36}.

Creams with anti-androgens have limited effectiveness. No benefit has been found with the use of 5% canrenone, the active metabolite of spironolactone. Studies have shown conflicting results with topical finasteride^{17,37}.

CHART 7: Progestins with androgenic activity

High androgenic activity	Low androgenic activity
Levonorgestrel Norgestrel	Norgestimate, Desogestrel Gestodene

Insulin sensitizers

These drugs reduce both hyperinsulinemia and hyperandrogenemia, in addition to their benefits on lipid profile, blood pressure and ovulation^{33, 38, 39}. The reduction in androgen levels occurs by direct influence on ovarian steroidogenesis through the decrease of insulin levels and increase of SHBG¹⁵. Treatment of hirsutism with these drugs is still controversial, although studies have shown reduced growth and thickness of hair, and improvement of acne and acanthosis nigricans^{15, 38, 40, 41}.

Metformin has been suggested as a first-choice drug in the treatment of hirsutism in women with PCOS, metabolic and reproductive disorders^{10, 15, 34}. The initial dose is 500mg at dinner, which may be increased every week until a maximum dose of 2000mg/day, divided into two doses¹⁰. The effect disappears 3 months after discontinuing the drug. The most frequent side effects are dose dependent, occurring nausea and diarrhea. Lactic acidosis is rare and insignificant when young subjects with PCOS are evaluated^{10, 27}.

These effects can also be obtained with pioglitazone and rosiglitazone, and they may be greater with the combination of oral contraceptive or flutamide^{40, 42}. However, the safety of treatment with these drugs still needs further evaluation. Patients should be informed of the chance of spontaneous ovulation.

Cosmetic treatment

Cosmetic procedures are important in the treatment of hirsutism, which may be sufficient to control mild to excessive hair growth or as an adjuvant in severe cases. Shaving, depilation or destruction of the dermal papilla by electrolysis or

laser may be performed. Hair removal using wax is discouraged for patients with more severe cases of hirsutism. This technique can be effective, but there is a risk of skin irritation, folliculitis and ingrown hairs. Laser epilation is the most effective method and, despite the high cost, requires fewer sessions and the results are better.

Eflornithine hydrochloride is an irreversible inhibitor of ornithine decarboxylase, which was recently released for topical use in the treatment of facial hirsutism. This enzyme is modulated by androgens and regulates cell proliferation in the matrix of the follicle. Studies have shown significant reduction in the amount of hair, but the effect is rapidly reversed after discontinuation of the drug. Topical retinoids like calcipotriene and keratolytic drugs, such as ammonium lactate, can be useful in the treatment of acanthosis nigricans, as long as hyperinsulinemia is controlled^{15, 43}.

Besides systemic treatment, alopecia can be controlled with topical minoxidil 2 or 5% and if necessary, with hair transplant^{23, 44}.

CONCLUSION

Polycystic ovary syndrome is a common endocrinopathy that affects women of reproductive age, which may cause metabolic disorders and psychosocial problems. Early diagnosis is essential for the prevention of complications and we should be attentive to the variety of clinical findings. Although its etiology has not yet been fully elucidated, knowledge and understanding of the abnormality in the hypothalamus-pituitary axis, steroidogenesis and insulin resistance are of utmost importance for early, effective and safe treatment. □

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