Chapter 2

Controversies in Polycystic Ovary Syndrome

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Additional information is available at the end of the chapter

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Abstract

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy that affects women from puberty to whole reproductive life. Diagnosis and treatment of PCOS is not clear. Polycystic ovary syndrome is a multisystem disease that involves dermatologist examining patients with clinical hyperandrogenism and/or biochemical signs of hyperandrogenism; gynecologist examines patients with oligo-ovulation or infertility. The management of PCOS should be tailored to each woman's specific symptoms, fertility-related implications, and metabolic disorders. Pharmacologic treatment is not necessary for all patients with PCOS, also lifestyle changes like exercise, weight loss, and diet are effective for treatment. Lifestyle changes are often recommended as first-line treatment for PCOS to benefit general health. Topical nonhormonal therapies and laser hair removal may be effective for cutaneous symptoms like acne, hirsutism, and androgenetic alopecia in the PCOS population and are useful first-line agents. Some pharmacological agents (anti-androgens) are used to control the dermatological symptoms of hyperandrogenism. Metformin is useful for metabolic and glycemic anomalies and for the treatment of menstrual irregularities, but less effective than antiandrogens for the treatment of both hirsutism and acne. The aim of this study is to talk about unclear topics in PCOS and multidisciplinary approach to patients.

Keywords: polycystic ovarian syndrome, hyperandrogenism amenorrhea, hirsutism, infertility

1. Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder among women of reproductive age but often unrecognized condition. It was first described by Stein and Leventhal in 1935 as women with polycystic ovaries, amenorrhea, and hirsutism [1]. One in

15 women worldwide is affected by this syndrome [2]. There is actually no consensus on diagnostic criteria and the figures may change.

Most women with PCOS have infertility or subfertility and other metabolic alterations such as insulin resistance, dyslipidemia, hyperinsulinemia, and obesity. Despite the etiology of the syndrome is still far from being elucidated, it could be considered the result of concurrent endocrine modifications, lifestyle factors, and genetic background. In particular, accumulating evidence suggests that insulin resistance and compensatory hyperinsulinemia play a pivotal pathogenic role in the hyperandrogenism of many PCOS phenotypes, which in turn have a clear detrimental effect on chronic anovulation [3].

There has been considerable controversy about specific diagnostic criteria when all classic features (hirsutism, irregular menstrual cycles, obesity, and a classic ovarian morphology by transvaginal ultrasonography) are not evident.

Research for PCOS in the last decade has brought new important insights for the evaluation and treatment of this disorder. Unclear points for diagnosis and treatment and proper approach to PCOS-related diseases will be discussed in this chapter.

2. Diagnosis

Some criteria have been proposed for the diagnosis of the disease but these criteria have changed several times. In fact, clinically recognized hyperandrogenism and the non-regularity of ovarian function, especially chronic anovulation, are the main criteria. Hirsutism, acne, and alopecia are clinical signs of hyperandrogenism in these women while it may be difficult to make a diagnosis due to phenotype, obesity, race/ethnicity, and environmental factors. Most of these women have polycystic ovaries that can be shown in imaging studies, but this is not a criterion for diagnosis because many healthy women may have polycystic ovaries. The diagnosis of the polycystic ovary was also revised. Most of the researchers used the presence of at least 12 follicles (measuring 2–9 mm in diameter) in each ovarian as a criterion prior to 2014. Dewailly et al. reported that the threshold value of ≥25 follicles is significant for diagnosis [4]. In addition, it is not uncommon for PCOS to coexist with obesity, insulin resistance, dyslipidemia, endothelial dysfunction, and other metabolic disorders. All of these suggests metabolic syndrome.

2.1. Diagnostic criteria

According to 1990 National Institutes of Health (NIH) criteria, hyperandrogenemia findings and ovulation disorder were defined as PCOS. In 2003, Rotterdam criteria for PCOS diagnosis were accepted by the NIH (**Table 1**) [5].

General agreement exists among specialty society guidelines that the diagnosis of PCOS must be based on the presence of at least two of the following three criteria: chronic anovulation, hyperandrogenism (clinical or biological), and polycystic ovaries [6].

	NIH 1990 criteria	Rotterdam criteria [5]	AE-PCOS Society criteria
Hyperandrogenism	Required	Two of three required	Required
Ovulatory dysfunction (oligo- or amenorrhea)	Required	Two of three required	Either ovulatory dysfunction or PCOS morphology required
PCOS morphology	Not required	Two of three required	Either ovulatory dysfunction or PCOS morphology required

Table 1. Diagnostic criteria for PCOS.

2.1.1. Detecting of ovulatory dysfunction

The definition of ovulatory dysfunction is not clear. If the menstrual cycle length is longer than 35 days, it is assumed that chronic anovulation is present and that special tests are not needed. A 30–35 day cycle can also be anovulatory. Measurement of serum progesterone in the mid-luteal stage (Days 21–22) is the best way to evaluate ovulation. Progesterone levels > 2.5 ng/mL may indicate ovulation but values of ≥7 ng/mL are needed for normal luteal function [7]. Three consecutive measurements with a total serum value of ≥15 ng/mL indicate normal luteal function. Alternatives to progesterone measurement such as baseline body temperature schedules, urinary luteinizing hormone (LH) kits, or timed endometrial biopsy may be suggested, but do not provide sufficient information about the luteal phase. The cycle time for oligomenorrhea is ≥35 days in adult women. The threshold value during puberty is higher and a cycle length of up to 40 days can be considered normal.

2.1.2. Measurement of androgens

In women, the androgen source is the adrenal cortex and the ovaries. Testosterone is produced from the ovary, DHEA-S is produced from the adrenal gland, and androstenedione is produced from both adrenal and ovarian.

The issue of which serum androgen should be measured for diagnosis of PCOS remains controversial. Free testosterone (T) levels are more sensitive than the measurement of total T for establishing the existence of androgen excess. The normal value of total testosterone level is 20–60 ng/dl. In cases with PCOS, the total testosterone level is generally lower than 150 ng/dl. If the total testosterone level is higher than 150 ng/dl, testosterone-secreting adrenal tumor, ovarian tumor, or ovarian hypertrophy should be suspected. In patients using oral contraceptives, total androgen levels should be measured 8–12 weeks after drug withdrawal.

Direct analog RIA measurement in commercial laboratories is notoriously inaccurate. Ideally, it should be determined through equilibrium dialysis techniques. Consequently, if the clinician is uncertain regarding the quality of the free-T assay, it may be preferable to rely on calculated free T, which has a good concordance and correlation with free T as measured by equilibrium dialysis methods [8]. Value of measuring levels of androgens other than T (dehydroepiandrosterone sulfate, androstenedione) in patients with PCOS is relatively insignificant. If dehydroepiandrostenedione sulfate (DHEAS) levels are higher than 700 μg/dL, adrenal tumors should be suspected. DHEAS levels may also increase in cases with LOCAH (late-onset congenital adrenal hyperplasia), Cushing's disease, adrenal adenomas as well as PCOS.

2.2. Other laboratory tests

Patients with non-classical 21-hydroxylase deficiency may develop as PCOS hyperandrogenism, anovulation, and PCO. Therefore, evaluation of serum 17 hydroxyprogesterone (17OH-PG) should be always included in a diagnostic study [9, 10]. Serum 17OH-PG levels higher than 10 ng/mL indicates the presence of 21-hydroxylase deficiency, while values between 2 and 10 ng/mL suggest that further testing with adrenocorticotropic hormone stimulation is needed [10]. Serum AMH > 5 ng/mL is also reported to be significant for PCOS [11].

2.2.1. Evaluation of ovarian morphology

Ovarian morphology is usually evaluated by transvaginal ultrasonography. Transabdominal ultrasonography may be used for virgin patients, but ovarian morphology assessment and especially the calculation of the number of small follicles may be difficult. Ultrasonographic imaging technology has been rapidly developing and the clinician should know that the number of follicles visible is related to ultrasound quality [4]. According to current Rotterdam guidelines, PCO is defined as the presence of at least 12 follicles measured 2–9 mm or an increased ovarian size (>10 mL) (**Figure 1**) [12]. The new AES guidelines, based on the observation of published data using new ultrasound technology, increased the threshold number of small ovarian follicles to 25 [4]. The ovarian size threshold is unaffected by new technologies and the threshold between normal and increased ovarian size is assumed to be 10 mL. In some populations, during puberty or aging, a different threshold for ovarian size may be suggested [13].

2.2.2. Clinical signs of hyperandrogenism

Hirsutism is defined as excessive hair growth in women in a manner consistent with androgen sensitivity. Typically, hirsutism in PCOS is followed by initial menarche, whereas in some of the adolescent girls, pubic hair development and hirsutism had already begun 25–33% of white women have terminal hair on the upper lip, periareolar area or linea-alba, but hirsutism and various other hyperandrogenic disorders are more prominent in PCOS. The presence of substantial numbers of terminal hairs over the chin, neck, lower face, and sideburns (particularly if extending medially) indicates the presence of androgen excess. It should be noted that ethnic differences in the number of hair follicles present and individual skin sensitivity of the

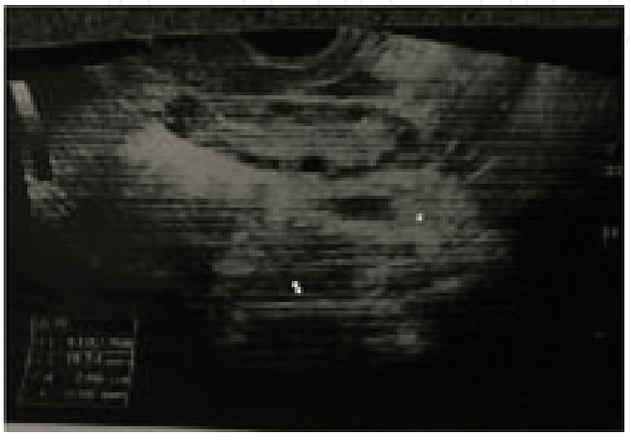

Figure 1. Transvaginal sonographic view of a polycystic ovary syndrome patient (Işık Kaban M.D. photo archive).

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pilosebaceous unit to androgens are major determinants of the presence of hirsutism, as well as acne and androgenic alopecia (**Figures 2–5**) [14]. Ferriman-Gallwey scale has been the most widely used for evaluating hirsutism, but it is limited by its subjective nature and failure to include the sideburn, perineal, or buttock areas [15]. In this system, nine regions in the body are

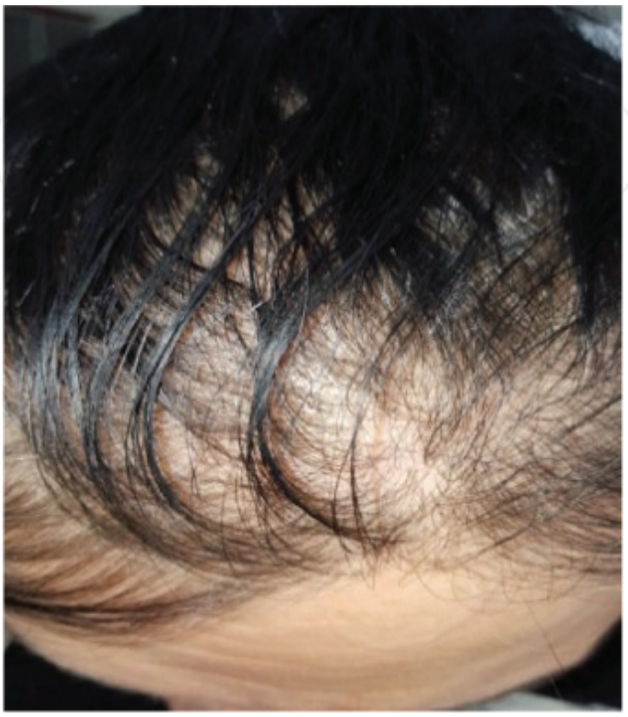

Figure 2. Androgenetic alopecia.

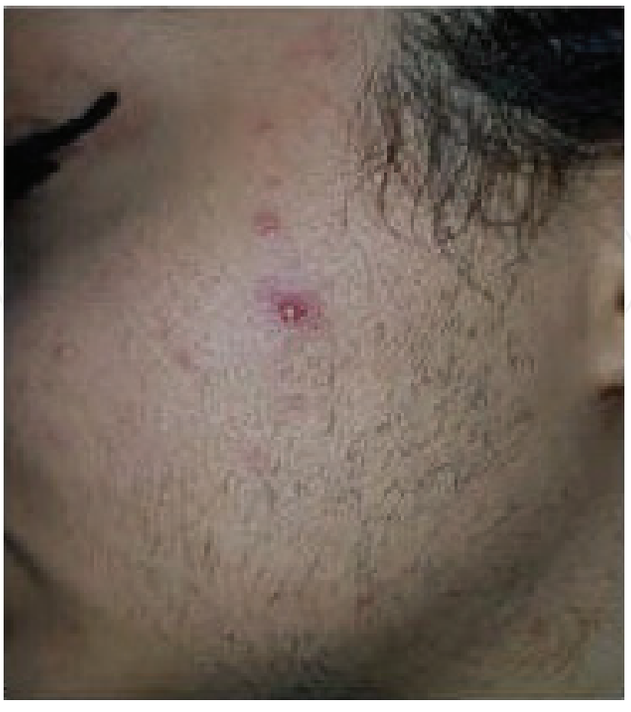

Figure 3. Acne and facial hirsutism.

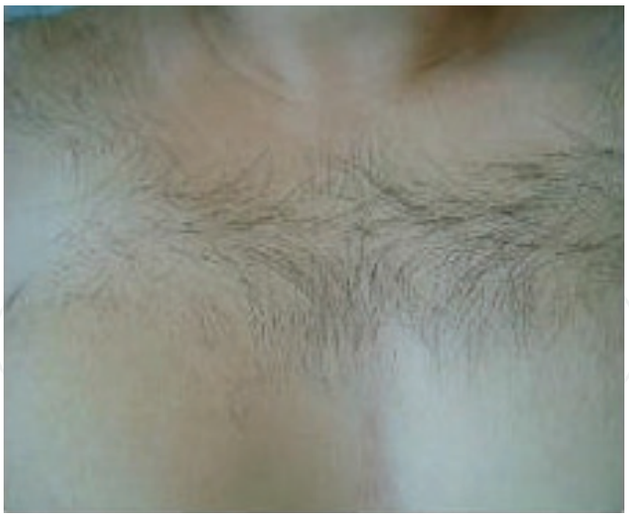

Figure 4. Hirsutism.

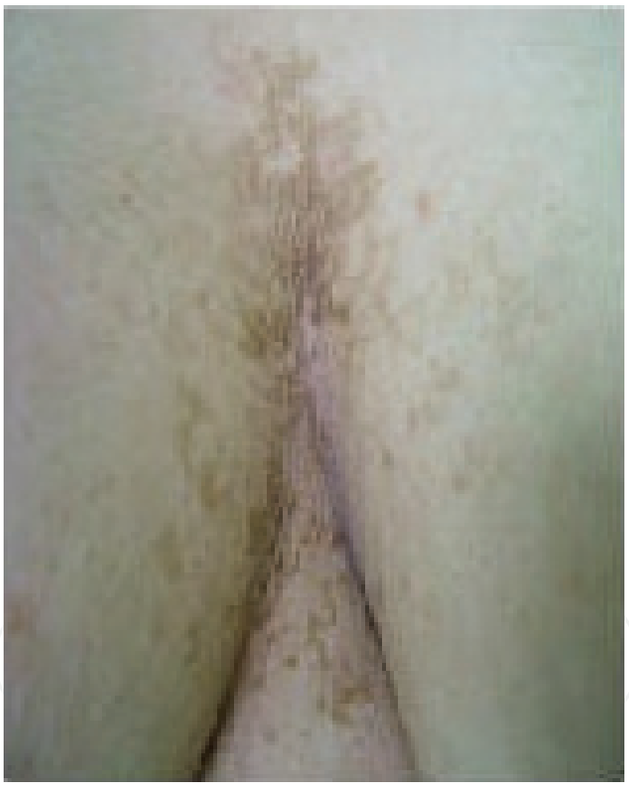

Figure 5. Acanthosis nigricans.

scaled from zero (no terminal hair) to four (excess hair). Above eight is regarded as hirsutism. Additionally, acne, androgenetic alopecia, and virilization indications (clitoromegaly, muscle mass increase, voice thickening, diminution of breast size, libido increase) should be examined.

Ferriman-Gallwey scoring system for hirsutism: upper lip, chin, chest, upper back, lower back, upper abdomen, upper arm, forearm, and thigh/leg are the body parts used for hirsutism diagnosis.

At this point, the differential diagnosis of these patients is important. Late-onset congenital adrenal hyperplasia (LOCAH) should be remembered especially in puberty patients. The use of drugs such as methyltestosterone, anabolic steroids (norethandrolone, etc.), phenytoin, diazoxide, danazol, cyclosporin, valproic acid, and minoxidil, which stimulate hair growth with androgenic effect, should be questioned. In terms of Cushing's disease, findings such as stria, central obesity, buffalo hump, and plethora should be investigated. Galactore should be investigated for hyperprolactinemia.

Acne is another clinical sign of hyperandrogenism. The likelihood of developing PCOS in girls with severe acne or acne resistant to treatment may be up to 40% in adolescents [16, 17]. In cases with persisting after adolescence, or aggravating by mid-20s, hyperandrogenemia is common and acne can be considered a clinical sign of hyperandrogenism. However, during adolescence, acne should not be considered a substitute for hyperandrogenism [18].

Only those with acne can have serum free T levels as well as those seen in hyperandrogenic disease states. Likewise, hirsutism without acne is also the case [17].

Hair loss in women with hyperandrogenism is variable. Women with severe hyperandrogenemia may experience bitemporal hair loss and loss of the frontal hairline [19].

2.2.3. Treatment options for women with hyperandrogenism

Some pharmacological agents (anti-androgens) are used to control the dermatological symptoms of hyperandrogenism. Oral contraceptive agents can effectively reduce the androgenic effect by increasing the sexual hormone binding globulin and/or suppressing ovarian production of androgens. In addition, physiologic doses of dexamethasone or prednisone may directly reduce adrenal androgen production. The basic mechanism of anti-androgen therapy is competitive antagonism of the androgen receptor or inhibition of 5α-reductase to prevent the conversion of testosterone to its more potent form, 5α-dihydrotestosterone. Spironolactone, cyproterone acetate, and flutamide are effective with competitive antagonism and finasteride is effective with the inhibition of 5α-reductase.

The mainstay of primary care is oral contraceptive therapy for dermatological problems in hyperandrogenism. Oral contraceptives contain estrogen (ethinyl estradiol) and a progestin. A 20–35 μg of daily ethinyl estradiol effectively suppresses pituitary-ovarian axis and reduces ovarian androgen production. The ideal progestin to be used in PCOS is progestins with the lowest androgenic profile such as chloramidon and drospirenone; however, these may induce venous thrombosis and are contraindicated in obese patients. Oral contraceptives induce the synthesis of sex hormone binding protein (SHBP) from the liver and may be more effective in controlling hirsutism and acne than transdermal or vaginal ring preparations. These formulations may be combined with anti-androgenic therapy to achieve a better response against hirsutism. Spironolactone is an aldosterone antagonist and widely used androgen blocker, its progestational activity may also reduce levels of the gonadotropin-releasing hormone. Spironolactone can induce hyperkalemia. Headaches and dizziness as side effects are relatively frequent, and the patient should increase water and salt intake during hot weather. Spironolactone can cause intermenstrual spotting in about half of women.

Finasteride is a 5α-reductase inhibitor and may decrease DHT levels by 50–60%. Significant anti-androgenic effects were shown after 6 months of treatment at 5 mg/day dose [20, 21]. The use of 5α-reductase inhibition therapy should be considered when the previous therapy with oral contraceptive and spironolactone is relatively ineffective [22]. Dutasteride, another anti-androgen molecule which has limited data, reduces plasma DHT more significantly than finasteride and inhibits the conversion of testosterone to dihydrotestosterone by the inhibition of 5α-reductase isoenzymes [23].

Metformin is an alternative therapy for hirsutism in women with PCOS who have other indications for the use of metformin. This oral antidiabetic drug is useful for metabolic and glycemic anomalies and for the treatment of menstrual irregularities, but less effective than antiandrogens for the treatment of both hirsutism and acne [22, 24].

It should be remembered that hirsutism treatment is a continuing treatment that the medical treatment response does not occur 6 months before the hair cycle and individualization of the treatment are necessary.

2.3. PCOS in the adolescent

PCOS commonly presents in the adolescence; underestimation may be more in this period because of some confounding factors such as acne, menstrual irregularities, and hirsutism [25]. These factors may also be observed in normal puberty thus misdiagnosis may be common. Anovulatory cycles and menstrual irregularities with variable cycle length are common during first years following menarche due to the immaturity of the hypothalamic-pituitary-ovarian axis. Additionally, large, multicystic ovaries in adolescents may also be considered normal as a result of natural ovarian development. It may be acceptable to clinically follow the patient for 2–3 years in terms of defining the over dysfunction in adolescents [26].

Hyperandrogenism leading to acne and hirsutism may be associated with normal puberty rather than underlying PCOS, and hyperinsulinemia is a characteristic of normal puberty. Furthermore, ranges of laboratory values for the hyperandrogenemia and Ferriman-Gallwey scoring system are established for adults and may not be of similar clinical importance in adolescence.

On the other hand, symptoms in adolescents are heterogeneous and may change over time, PCOS diagnosis may be overlooked.

In conclusion, clinical findings for PCOS in adolescents can be confusing and laboratory measurements are important. Lower and upper bounds of testosterone are not clear in young girls [25, 27].

2.4. PCOS and malignancy

A relationship between PCOS and malignancy has been reported in the literature, but this relationship is not strong. The altered metabolic and hormonal environment among women with PCOS may increase the risk of some types of cancer.

In a systematic review by Chittenden and colleagues, they investigated the gynecological malignancy association with PCOS and reported that women with PCOS are more likely to develop endometrial cancer (odds ratio 2.70) and ovarian cancer (odds ratio 2.52) but not breast cancer [28]. John et al. compared 919 women with PCOS and 72,054 women without PCOS in their meta-analyses and reported that women of all ages with PCOS have an increased risk of endometrial cancer (odds ratio 2.79), but the risk of ovarian and breast cancer was not significantly increased overall [29]. Another meta-analysis by Holly et al. reported that the associations between PCOS and endometrial, ovarian, and breast cancer are complex [30] and argued that studies showing PCOS association with endometrial cancer do not take into account body mass index (BMI) criteria. BMI is a strong and well-established risk factor for endometrial cancer. In these women, the oligomenorrheic environment increases hyperplasia and cancer risk. Prevention of oligomenorrhea by providing cyclic progesterone supplementation is important for reducing risk [31].

As a result, the risk of endometrial cancer in women with PCOS may be increased [32]. However, there is no clear association between other types of cancer and PCOS.

3. Dermatological approach to polycystic ovarian syndrome

Polycystic ovary syndrome is a multisystem disease that involves dermatologist examining patients with clinical hyperandrogenism and/or biochemical signs of hyperandrogenism; gynecologist examines patients with oligo-ovulation or infertility.

Although PCOS is a heterogeneous disorder without an easily identified single etiology, the key pathophysiologic components appear to include androgen excess, abnormal gonadotropin dynamics, and insulin resistance. Patients should be informed about long-term treatment, including lifestyle changes with systemic treatment. Success in effective management of women with PCOS is a synchronized effort between dermatologist, endocrinologist, obstetrician, nutritionist, and physical trainer [33].

4. Treatment

Lifestyle changes, local treatment approaches, and pharmacological treatment will review under the heading of treatment.

In cases with PCOS, lifestyle modification resulting from medical nutrition therapy and exercise is effective in improving clinical signs and symptoms of hyperandrogenemia. With lifestyle changes, SHBG levels increase as serum androgen levels decrease as a result of weight loss. Stop smoking is also important to reduce the complications of oral contraceptive use [33].

Local treatment; hair removal methods such as hair bleaching, tearing, shaving, waxing, electrolysis, laser hair removal, and local drug application such as eflornithine are used. It can be applied as a single treatment in the case of localized small incisions. Medical treatment is applied when waiting for the response. It has been shown that shaving does not increase the formation of

new hair, and it should be explained that the illness should not underestimate this concern. It has been shown that laser epilation can treat up to 2 years hirsutism in randomized controlled trials. Since hair follicle stimulation continues in hyperandrogenic women, hair growth after laser epilation repeats. About 13.9% eflornithine topical cream inhibits DNA synthesis by inhibiting ornithine decarboxylase enzyme and suppresses the mitotic activity of the hair follicle. Terminal hair growth begins again when the drug is stopped.

Patients with polycystic ovarian syndrome are referred to clinics of dermatology with cutaneous androgenesis findings such as hirsutism, acne, and alopecia. For this reason, pharmacological treatment is often required to treat hyperandrogenemia. It should be remembered that hirsutism treatment is a continuing treatment, which the medical treatment response does not occur 6 months before the hair cycle and individualization of the treatment is necessary. Treatment may not be necessary for the patients who do not worry about hirsutism, planning to be pregnant, and regular menstrual cycles. OCSs are used as the only medication in mild hirsutism cases, while OCSs are used in combination with other antiandrogen drugs in severe and moderate hirsutism. Hirsutism adolescent girls respond perfectly to medical treatment. The combination of spironolactone and an oral contraceptive provides effective medical treatment. This combination also improves spironolactone-related menstrual irregularities. If there is no response after 6 months of treatment, the treatment should be changed. The combination of mechanical and medical treatment provides a rapid and effective remedy. The average duration of treatment is 2–3 years. Because the underlying cause is persistent, local or drug treatment does not completely cease, and the complaints start again after the treatment is discontinued.

Insulin-sensitizing drugs (metformin and pioglitazone) are used in the treatment of hyperandrogenemic patients with severe insulin resistance syndrome. It should not be used as a primary treatment in incontinent cases. Metformin is preferred for patients with PCOS with glucose intolerance. In these cases, metformin may contribute to other treatments on hirsutism. Glitazones are not recommended for treatment of hirsutism due to possible cardiovascular side effects. It is the first choice in the treatment of menstrual and ovulatory dysfunction, especially in obese cases of lifestyle change and weight loss.

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