Hirsutism Acne and Hair Loss: Management of Hyperandrogenic Cutaneous Manifestations of Polycystic Ovary Syndrome

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ABSTRACT

Polycystic ovary syndrome is the most common endocrine abnormality that affects reproductive-aged women. Diagnostic criteria of polycystic ovary syndrome have been established by different societies in recent years, and hyperandrogenism remains as one of the main criteria for diagnosis. Cutaneous manifestations of hyperandrogenism include hirsutism, acne and androgenic alopecia and are commonly observed in women with polycystic ovary syndrome. The major determinants of cutaneous manifestations are increased production of androgen and increased tissue availability. Cutaneous manifestations of hyperandrogenism are cosmetic problems, which produce significant emotional distress and psychological morbidity. Treatment includes a combination of combined oral contraceptives, antiandrogens, insulin sensitizers, gonadotropin releasing hormone agonists, topical medications, and cosmetic procedures. The diagnosis, management, and treatment approaches are described in detail in this review.

Keywords: Acne, Hirsutism, Allopecia, Hyperandrogenism, Cutaneous manifestation, Polycystic ovary syndrome

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Introduction

Polycystic ovary syndrome (PCOS) is the most prevalent endocrinologic disorder among reproductive-aged women. The reported prevalance of PCOS in women of this age group varies from 6-15% depending on which diagnostic criteria are used to define the syndrome (1). There is accumulating evidence that a high androgen level is the fundamental factor in the pathogenesis of PCOS (2). Although there is considerable heterogeneity in the clinical features among women with PCOS, clinical manifestations of hyperandrogenism, including hirsutism, acne, and androgenic alopecia are consistently cutaneous manifestations of this disease (3,4). Forty percent of women with PCOS may have no hyperandrogenic symptoms on presentation (5). Clinicians should be aware of the impact of hyperandrogenic symptoms on a woman's self-image perception and the subsequent psychological effects.

The development of the cutaneous features in PCOS is quite complex. Androgens have a major role in the development of these symptoms. Hypothalamic dysfunction, which plays a role in the pathogenesis of PCOS, results in an increased ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH). This increased ratio promotes theca cells of the ovary to preferentially synthesize androgens (6). In addition, the hyperinsulinemic state of PCOS enhances androgen production by the theca cells and inhibits hepatic synthesis of sex hormone binding globulin (SHBG), which results in an increase in unbound and active androgen levels (7). However, cutaneous manifestations of androgen excess can be seen in the absence of biochemical hyperandrogenism (8).

All current definitions of PCOS require that other disorders of androgen excess or ovulatory function be excluded. It is critical to rule out alternative causes of androgen excess such as late-onset congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting tumors and drug-induced or iatrogenic hyperandrogenism; the latter includes thyroid dysfunction and hyperprolactinemia. Signs of virilization, such as lowered voice tone, temporal balding, increased muscle mass, and clitoromegaly, should prompt evaluation for an androgen-secreting tumor of the adrenal gland or ovary. Laboratory studies in patients with suspected PCOS are ordered to document hyperandrogenism biochemically and rule out late- onset congenital adrenal hyperplasia. A serum 17-hydroxyprogesterone level less than 2 ng/mL will effectively exclude late-onset congenital adrenal hyperplasia. If the 17-hydroxyprogesterone level exceeds 2 ng/mL, an adrenocorticotropic hor-

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mone (ACTH) stimulation test is the next step and a level more than 10 ng/mL confirms diagnosis. Laboratory tests to document hyperandrogenism include total and free testosterone and dehydroepiandrosterone sulphate (DHEA-S). A patient with clinical findings of Cushing's syndrome should be evaluated with a 24-hour urinary free cortisol test. Thyroid dysfunction and hyperprolactinemia can be excluded by routine measurement of thyroid-stimulating hormone (TSH) and prolactin levels, although the prevalence of these disorders in women with overt hyperandrogenism is relatively low (9).

HIRSUTISM

Hirsutism is defined as growth of the terminal hairs in a male pattern, on the face, neck, chest, upper arms, abdomen, gluteal area, and inner thigh. In these androgen sensitive areas, with the effect of androgens on pilosebacous units; fine, non-pigmented, short vellus hairs that are normally present transform into coarse, stiff, and dark terminal hairs. This should be differentiated from hypertrichosis, where hair growth is not dependent on androgens and hairs are not distributed in a male pattern. Race, ethnicity and 5α-reductase activity play important roles in genesis of hirsutism. Both sensitivity of skin and increased production of androgen determines the level of hirsutism.

Hyperandrogenism most often primarily presents as hirsutism in clinical practice and among the hyperandrogenism symptoms, hirsutism is the one that is most dependent on androgens. Hirsutism is the second most common manifestation of PCOS after oligomenorrhea. Even in the presence of regular cycles, PCOS is the most common cause of hyperandrogenism and hirsutism (10). The prevalence of hirsutism in PCOS varies according to geographic and racial characteristics; therefore, a wide range (40-92%) has been reported in American and European women (5, 11). However, the severity of hirsutism is not reflected by circulating androgen levels and can vary considerably within and between individuals.

The presence and severity of hirsutism is objectively quantified according to a visual score system, most commonly by a modified Ferriman-Gallwey score (12). Nine body areas are assigned a score of 0-4 based on the density of terminal hairs. A score of 0 represents the absence of terminal hairs and 4 represents extensive terminal hair growth. Hirsutism is generally determined as a score of 8 or above, although some have used a cut-off value of 6 (13, 14). Although hirsutism is determined with scores of 6-8 or above, most women with lesser scores consider themselves to be hirsute and seek treatment because they are distressed by their hair growth. Whether additional testing is needed to exclude other causes of hyperandrogenism is determined from the patient's history and their physical examination. The initial evaluation should be aimed at questioning the likelihood of PCOS as the cause of hirsutism. Other factors that should be determined are the age of menarche, menstrual regularity, fertility history, presence of other hyperandrogenic symptoms, distribution of increased hair growth, voice changes, presence of buffalo hump, and decreased vaginal secretions. Rapid onset, severe and progressive symptoms must be screened extensively for androgen-secreting tumors.

Treatment

Hirsutism can be one of the most distressing symptoms among all symptoms associated with PCOS. Excessive facial or body hair can be a particularly symptomatic due to the negative impact on perceived femininity. The decrease in self-esteem exacerbates women's perception of the problem, which increases the tolerance for the regular need of cosmetic management of hirsutism.

Milestones in the management of hirsutism include correction of the hormonal imbalance, slowing or stopping hair growth, improving quality of life and esthethic appearance of the women. Although medical methods improve hirsutism, they do not produce the complete elimination that women desire and drug treatment is often palliative rather than curative. This means that hirsutism becomes less intense and the time interval between cosmetic interventions increases. Also, clinicians should be aware that the patient's assessment of her response to therapy is the most important outcome. At each follow-up visit, the patient should be asked whether there has been any decrease in the need for cosmetic treatment to manage her hirsutism. Treatment is long term and due to the length of the hair growth cycle, the effects of medical therapy may not be evident for up to 6 months after administration and the maximal effect may not be known for 9 to 12 months (15). At the end of six months, the patient should be asked whether she feels there has been optimal decrease in hair growth. If not, a change in dose or drug, or combination with other agents might be considered. There is no clear single therapy for hirsutism in PCOS. In general, a combination of medical treatment with a variety of cosmetic approaches appears to produce the best results.

Pharmacologic treatment

Combined oral contraceptives

Generally, combined oral contraceptives are considered as the first-line therapy in PCOS- related hirsutism due to their safety and cost-effectiveness. The estrogen component of oral contraceptives suppresses LH secretion, which decreases ovarian androgen biosynthesis. The estrogen component also increases hepatic synthesis of SHBG, which leads to a decrease in biologically available testosterone (16). Moreover, combined oral contraceptives induce a moderate decrease in adrenal androgens through direct interaction with adrenal steroid biosynthesis (17). The primary effect of combined oral contraceptives on hirsutism is the reduction in the development of new terminal hairs. Fully terminalized hairs do not disappear, but with therapy, some extent of terminal hairs may get thinner and grow slower. Although current combined oral contraceptives contain relatively low levels of estrogen, the metabolic effects of combined oral contraceptives are mainly determined by the progestin component. Progestins have some

degrees of androgenic effects. Additional anti-androgenic properties are present in the progestin component of some combined oral contraceptives such as drospirenone, cyproterone acetate, dienogest, clormadinone acetate, and those with a low androgenic potential, which are called as 'third generation progestins', desogestrel, norgestimate, and gestodene (18). It is preferable to choose a progestin with low androgenicity or with an anti-androgen property in the therapy of hirsutism. According to studies that compared outcomes of different types of oral contraceptives, there is no superiority of one compound over another in the treatment of hirsutism in women with PCOS (19). When comparing cyproterone acetate in doses greater than 2 mg (doses ranging from 25 to 100 mg) in addition to ethinyl estradiol with the lower dose of 2 mg in combination with ethinyl estradiol, all resulted in subjective improvement of hirsutism (20). Similar efficacy was observed in a study on a group of adolescents with hirsutism that compared 0.15 mg desogestrel plus 30 μg ethinylestradiol with 2 mg cyproterone acetate plus 35 μg ethinylestradiol (21). A comparative study of combined oral contraceptives, drospirenone and ethinylestradiol versus 2 mg cyproterone acetate and 35 μg ethinylestradiol, demonstrated a similar efficacy between the two formulations in reducing hirsutism (22). However, a combined oral contraceptive that contained 2 mg chlormadinone acetate and 30 μg ethinyl estradiol was found to be less efficacious in reducing hirsutism compared with one that contained 3 mg drospirenone and 30 μg ethinylestradiol (23). A recent study that compared the effects of combined oral contraceptives containing cyproterone acetate, desogestrel and drospirenone on hirsutism showed no difference at six months; however, a cyproterone acetate/ ethinyl estradiol combination had a marked effect on hirsutism, beyond those of other combinations, after 12 months of therapy (24).

Anti-androgens

Anti-androgens are often considered a second-line therapy in hirsutism related with PCOS, especially in the setting of those patients who cannot use combined oral contraceptives or who do not have an adequate response after at least 6 months of treatment (16). The use of anti-androgens alone is not considered appropriate because of the potential adverse effects to the genitalia of the male fetus in utero, instead these drugs should be taken with reliable contraceptive methods in sexually active women. However, anti-androgens may be considered as a single-agent therapy in women who cannot conceive, or who are using effective contraceptive methods. Although some observational studies conclude that a one-third reduction in hirsutism with combination therapy of anti-androgens and combined oral contraceptives is accomplished, a benefit of combination therapies of anti-androgens with combined oral contraceptives over combined oral contraceptive monotherapy has not been demonstrated in controlled studies (25).

Spironolactone

Spironolactone is an aldosterone antagonist that prevents dihydrotestosterone from binding to its androgen receptor; it directly inhibits 5-alpha-reductase, and inhibits enzymes involved in androgen synthesis in the ovary and adrenal glands. The usual starting dosage of spironolactone is 25 to 100 mg twice daily, and the dose is titrated once every three months to achieve the desired effect, which may be noticeable within 2 months, but not later than 6 months (26). Postural hypotension, headaches, gastritis, hyperkalemia and menorrhagia are the associated adverse effects. Inter-menstrual bleeding can occur due to its progestin-like effects. To decrease the incidence of this bleeding, combined oral contraceptives may be used or the drug may be administered from days 4 through 21 of the menstrual cycle. Care with use must be taken in renal failure due to the risk of hyperkalemia. A Cochrane review that included nine trials, evaluated the effects of spironolactone vs. placebo, combined oral contraceptives and combination therapies (27). The review concluded that studies addressing this subject were scarce and small; spironolactone at a dose of 100 mg showed subjective improvements when compared with placebo. Spironolactone is synergistic if added to combined oral contraceptives and could provide some additional significant clinical benefit in the treatment of hirsutism in women with PCOS (28, 29). Because of risk of male pseudohermaphroditism for the fetus, it should be used together with an effective means of contraception.

Finasteride

Finasteride, a 5 α-reductase inhibitor, blocks the conversion of testosterone to the more potent dihydrotestosterone at the hair follicle. It is prescribed at a dosage of 5 mg daily for the treatment of hirsutism. Also, clinicians should recommend women to avoid pregnancy because of the risk of feminization of the male fetus. Finasteride does not appear to be as effective as spironolactone in the treatment of hirsutism (27). However, finasteride has shown equivalent efficacy to cyproterone acetate and ehinyl estradiol combinations in small studies (30). A study that investigated the addition of finasteride to an ethinyl estradiol/cyproterone combination reported a double-positive effect on hirsutism improvement (31). Although there is little experience with long-term treatment with finasteride, this drug has few adverse effects and is well tolerated. Due to its well-documented teratogenic effects, reproductive-aged women should not use this medication without taking adequate contraceptive measures.

Flutamide

Flutamide is a non-steroidal androgen receptor blocker that has been used for the treatment of hirsutism at a dosage of 250-500 mg daily. The use of flutamide treatment is limited because of its potential for life-threatening hepatotoxicity (32). A comparative study of finasteride 5 mg/day, flutamide 125 mg/day, and a combination of both treatments demonstrated that flutamide alone was more effective in the treatment of hirsutism than finasteride alone, and the combination of these drugs was no better than flutamide alone over a 12-

month period (33). In addition, a comparative study that examined the efficacy of flutamide demonstrated that flutamide was more effective than spironolactone in the management of hirsutism (34). If administered at a low dosage (less than 125 mg/day) hepatic dysfunction is rare while the long-term efficacy on hirsutism is preserved. (35).

Cyproterone acetate

Cyproterone acetate is a progestin that reduces ovarian androgen production through decreasing LH levels. It competes with dihydrotestosterone for binding to its receptor and shows peripheral activity. Cyproterone acetate is found as the progestin component of combined oral contraceptives at a dose of 2 mg or at higher doses (50 mg to 100 mg) in monotherapies or with combined oral contraceptives. Due to its strong progestin activity, it should be given between the 5th and 15th day of the cycle and combined with estrogens to prevent menstrual irregularity (36). A systematic review that compared the use of cyproterone acetate alone or in combination with ethinyl estradiol in the treatment of hirsutism demonstrated that cyproterone acetate was effective in reduction of hair growth (20). Also in that review, cyproterone acetate was compared with other treatments including ketoconazole, spironolactone, flutamide and gonadotrophin releasing hormone (GnRH) analogues, and no difference in clinical outcome was shown (20). As with other anti-androgens, appropriate contraception should be used during treatment because the drug can cause feminization of the male fetus.

Drospirenone

Drospirenone, a derivative of 17-α- spironolactone, is a progestin that has a weak anti-androgenic effect (37). Drospirenone is normally found in combined oral contraceptives at a dose of 3 mg. In studies that evaluated the effects of ethinyl estradiol/drospirenone in women with PCOS, an improvement in menstrual cycles, hirsutism, and acne has been observed (38, 39).

Insulin-sensitizing drugs

Treatment of insulin resistance by using metformin or thiazolidinediones has been demonstrated to reduce androgen levels and restore ovulatory function in many women with PCOS (16, 40). However, its effectiveness in the treatment of PCOS-related hirsutism is less clear. PCOS-related hirsutism may improve modestly with the use of rosiglitazone and metformin has minimal or no benefit (41).

Gonadotropin releasing hormone agonists

GnRH agonists effectively suppress ovarian hormone secretion; however, in the management of hirsutism, estrogen plays a major role. This therapy is usually combined with combined oral contraceptives because treatment with GnRH agonists result in hypoestrogenism. This therapy is not cost effective when compared with other treatments; consequently, GnRH agonists are rarely used to treat PCOS-related hirsutism. GnRH analogs should be reserved for use in women who do not respond or tolerate combined hormone therapies in the management of severe hirsutism. A study that compared the effectiveness of leuprolide and leuprolide plus ethinyl estradiol/ cyproterone acetate containing combined oral contraceptives demonstrated that both treatments were effective in patients with moderate to severe hirsutism (42).

Topical treatment

Topical eflornithine hydrochloride is used for the treatment of hirsutism. This agent inhibits orthinine decarboxylase, which is an enzyme responsible for hair follicle growth and proliferation. Topical administration does not remove hairs, it only reduces hair growth. After 24 weeks of treatment with twice-daily applications, 58% of women's hirsutism improved with treatment and one third were considered a clinical success (43). More rapid hair removal was demonstrated when combined with laser therapy (44).

Nonpharmacologic treatment

Life style modifications

Obesity is related to decreases in sex-hormone binding globulin levels and increases in unbound androgens. There is a functional hyperandrogenism related with visceral fat, particularly with central obesity in women. Obese women with polycystic ovaries who lose more than 5% of their initial body weight have a significant improvement in hirsutism.

Cosmetic measures

Bleaching, shaving, waxing and chemical depilation are effectively used to remove unwanted hairs temporarily either alone or in combination with drug therapy. These hair removal techniques are effective, easy, cheap and quick. However, these procedures can cause skin irritation, scarring, pain, folliculitis, hyperpigmentation, and ingrown hairs.

Permanent hair reduction

These techniques include electrolysis and photoepilation (laser or intense pulsed light) and are known as permanent hair reduction. In electrolysis, repeated treatments are required to accomplish permanent results; therefore, it can be time consuming. Electrolysis can result in post-inflammatory changes, ingrown hairs, pigmentation, and scarring.

In the last decades, a number of photoepilation methods have been introduced that can achieve permanent reduction of hair. These modalities target melanin in the hair bulb and aim to destroy hair follicles in the anagen phase. Therefore, ideal patients for these methods are those with light colored skin and dark hair. Multiple sessions are required to achieve a significant reduction. A number of laser systems are available for the treatment of hirsutism, the most commonly used are the ruby laser (694 nm), the diode laser (800 nm), the alexandrite laser (755 nm), and the neodymium:YAG laser (1064nm). Intense pulsed light epilation uses a flash-lamp with a high intensity polychromatic light filter to produce light with specific wavelengths. In a systematic review that compared the results

of laser and intense pulsed light in the treatment of hirsutism reported that alexandrite and diode lasers achieved better results than intense pulsed light with ruby lasers and neodymium:YAG lasers (45). In the literature, there are no long-term follow-up studies; however, long-term efficacy of permanent hair reduction methods has not been reported. Pain, redness, pigmentation, and swelling are the adverse effects of laser treatment. Suppressing endogenous androgenic activity with systematic pharmacologic treatment decreases hair growth in patients with hyperandrogenemia-like PCOS (36).

ACNE

Acne is a multifactorial, androgen-dependent disorder of pilosebaceous unit. Acne tends to occur on, but not limited to, the face and upper trunk. Androgens stimulate sebocyte proliferation in the pilosebaceous unit, which leads to altered sebum production especially in the facial region. However, androgens also increase the rate of mitosis and epithelial proliferation in pilosebaceous unit, which leads to hyperkeratosis and obstruction of the sebaceous follicle. Colonization of the pilosebaceous unit with Propionibacterium acnes occurs with the increase in the release of pro-inflammatory cytokines, which leads to inflammation. All of these events have a role in the development of clinical acne. Acne can manifest in non-inflammatory or severe inflammatory forms.

Androgens play a central role in the pathogenesis of acne. Although acne is less common in PCOS than hirsutism, it is also a sign of hyperandrogenism. The prevalence of acne in women with PCOS has been reported to be in the range of 9.8-66% (46-48). Androgens promote sebum production and cause abnormal follicular turnover (49). Although patients with acne commonly have normal hormone levels, some can have increased free testosterone and DHEA-S along with decreased levels of SHBG (50). Testosterone is converted in the skin by 5-α-reductase to DHT, which leads to sebaceous gland stimulation. Differential expression of 5-α-reductase in sebaceous gland has been offered as an explanation for the majority of patients having normal circulating level of androgens (51).

Treatment

The targets of treatment are to decrease sebum secretion, to reduce Propionibacterium acnes, to prevent comedogenesis and to restore the hormonal milieu. Treatment regimens should be simple and individualized according to the severity and presence of inflammatory acne. A combination of topical treatments and antimicrobials generally fail to reduce the amount and severity of acne in most women with PCOS. Hence, these patients have marked androgen dependent seborrhea. Many patients require long-term treatment due to chronic hyperandrogenism in PCOS. It is important to inform patients that there will not be much improvement for several months and subsequent follow-up visits every 4 weeks are essential, in which the aim of treatment and nature of preparations being used should be explained. It is important to be aware of higher rates of treatment failure; for acne management of women aged over 25 years, 82% fail multiple courses of systemic antibiotics and 32% relapse after isotretinoin (52). In light of current data, dietary factors have little effect on development of acne. Because many cosmetics have an aggravating effect on acneiform changes, water-based products should be used and make-up should be avoided.

Systemic therapies

Various systemic therapies are available for the management acne related to PCOS including corticosteroids, isotretinoin, antibiotics and contraceptives. Due to higher sebum excretion rates, the response to systemic therapies is mostly poor. Although combinations of systemic and topical antibiotic treatments are initially started, hormonal treatments accomplish an effective manipulation of acne in patients with PCOS regardless of whether serum androgen levels are high or low (53). Androgen suppression in the sebaceous gland is targeted with hormonal treatment, which should be used as first-line treatment in moderate-severe acne, or in those with symptoms of hirsutism and androgenic alopecia.

Oral antibiotics

Oral antibiotics have been used for the treatment of widespread acne and acne refractory to topical treatments. There are no clear conclusions about which antibiotics are the most effective or whether oral antibiotics are more effective than topical antibiotics (54). Tetracyclines and macrolides are the most employed drugs in the management of acne. Generally, 6-8 weeks are required for effective treatment. Combination oral antibiotics may increase the risk of bacterial resistance; however, when they are used in combination with benzoyl peroxide, bacterial resistance decreases.

Combined oral contraceptives

The mainstay of therapy for the women with PCOS includes combined oral contraceptives. This treatment option has the advantage of regulating the menstrual cycle and providing contraception. Most combined oral contraceptives achieve 55% reduction of total acneiform lesions (55). The estrogen component of combined oral contraceptives suppresses activity of the sebaceous gland and decreases the production of ovarian and adrenal androgens. Estrogens also increase the synthesis of SHBG from the liver and decrease the serum levels of free testosterone. Also they inhibit 5-α-reductase enzyme and prevent conversion of weaker androgens to potent androgens. Most of the used combined oral contraceptives today contain a lower dose of estrogen, although a higher dose of estrogen is needed to an exert effect on sebum production. Their efficacy is attributed mostly to the estrogenic component but recently the lower androgenic, also anti-androgenic progestin component of combined oral contraceptives increases efficacy on the management of acne. Progestins bind to both progesterone and androgen receptors, thus first- and second-generation progestins may aggravate acne (56). Third-generation progestins, desogestrel, norgestimate and gestodene, bind more selectively progesterone receptors and thus

may have beneficial effects on acne by minimizing androgenic effects.

However, a review of combined oral contraceptives used to treat acne demonstrated that all combined oral contraceptives were effective in reducing inflammatory and non-inflammatory facial lesion counts, severity grades, and self-assessment scores compared with placebo, and found few important differences between different combined oral contraceptives (57).

Anti-androgens such as cyproterone acetate in the form of combined oral contraceptives have a high efficacy in the treatment of recalcitrant acne in PCOS (11). Drospirenone, a progestin derivative of spironolactone, has anti-androgenic and anti-mineralocorticoid activity, through it improves acne (58). In a study that compared combined oral contraceptives containing drospirenone and triphasic combined oral contraceptives containing ethinyl estradiol/ norgestimate demonstrated that drospirenone containing oral contraceptives were superior in the treatment of acne and had comparable efficacy to the ethinyl estradiol/cyproterone acetate combination pill (59). The results of a study that compared dienogest plus ethinyl estradiol with cyproterone acetate plus ethinyl estradiol and placebo, showed that both preparations were superior to placebo and equivalent in mild to moderate acne over six cycles (60).

The effects of other estrogen-containing contraceptives such as transdermal patch and vaginal ring on acne has not been studied.

Antiandrogens

Cyproterone acetate

Cyproterone acetate is a progestational anti-androgen that blocks the androgen receptor. Cyproterone acetate interferes with gonadotropin secretion, though it also inhibits ovulation and reduces serum androgen levels. It also inhibits binding of dihydrotestosterone to its receptor and reduces activity of 5-α-reductase. To avoid menstrual irregularities, cyproterone acetate should be administered on the first day of the menstrual cycle and used for 10 or 15 days. The recommended dosage is 2-100mg daily, most commonly combined with ethinyl estradiol in the form of oral contraceptives, and this has been reported to be effective in the treatment of acne in women (61). Higher doses have been found to be more effective than lower doses; an overall improvement in acne has been reported in up to 90% of women treated with high dosages such as 50-100 mg daily (62).

Spironolactone

Spironolactone is an androgen receptor blocker and also an inhibitor of 5-α-reductase. Spironolactone can reduce sebum excretion by 30-50% (63). Recommended dosages for typical acne range from 25 mg to 200 mg daily. A randomized, placebo-controlled double-blind trial evaluating the effectiveness of 200 mg spironolactone in acne compared with placebo concluded that spironolactone significantly reduced the number of inflamed lesions (64); however, a Cochrane review on the use of spironolactone in acne demonstrated that spironolactone was not effective in acne (27). Increased efficacy has been shown when spironolactone is added to combined oral contraceptives (65). Combined oral contraceptives used in conjunction with spironolactone results in a decrease in adverse effects such as dysmenorrhea, irregular menses and breast tenderness.

Flutamide

Flutamide is a nonsteroidal peripheral androgen antagonist usually used in the treatment of prostate cancer. In a comparative study that evaluated the efficacy and tolerability of flutamide combined with a triphasic combined oral contraceptive concluded that flutamide induced a significant decrease in seborrhea and acne scores in patients with PCOS (66). In a study investigating the effects of flutamide and spironolactone on acne, superior efficacy was reported with flutamide at reducing total acne count and seborrhea at 3 months (34). Flutamide's use is not advocated in acne because the risk of fatal hepatotoxicity has been shown with dosages higher than 500 mg daily (67).

Insulin-sensitizing drugs

Minimizing insulin resistance is one of the main concerns in the management of PCOS. Metformin is the established oral insulin sensitizing agent. A systematic review of the studies that assessed hyperandrogenic symptoms and compared metformin with combined oral contraceptives concluded that limited data demonstrated no evidence of difference between metformin and combined oral contraceptives on acne (68).

Gonadotropin-releasing hormone agonist

GnRH agonists, such as leuprolide, buserelin or nafarelin, inhibit androgen production in the ovary by disrupting cyclical release of follicle-stimulating hormone and luteinizing hormone from the pituitary. Injectable and nasal spray forms can be given and have been determined to have a reducing effect on acne, with or without endocrine abnormality (69). Treatment with GnRH agonists is associated with menstrual symptoms, headache, and bone loss.

Topical therapies

Topical retinoids

To prevent comedogenesis and to treat existing comedones, topical retinoids should be administered as a first-line therapy. Depending on the severity of acne, topical retinoids can be used alone or in combination with other agents such as topical or oral antibiotics and benzoyl peroxide. Topical retinoids have a comedolytic action hence they normalize desquamation of keratinocytes, and they also have intrinsic anti-inflammatory properties. Patients should be informed that improvement may be delayed for 2 to 3 months after starting therapy. Their major adverse effects are dryness, erythema, and irritation. Topical retinoids increase the sensitivity of the skin to the sun and predispose to sunburn. Topical retinoids are contraindicated in

pregnancy due to possible teratogenic results and effective contraception should be considered in the reproductive-age group. Oral retinoids are used for severe cystic acnes.

Topical antimicrobials

For treatment of mild to moderate inflammatory lesions, topical antimicrobials and topical retinoid or benzoyl peroxide are usually employed. Topical antibiotics that have been used effectively in the management of acne include erythromycin, clindamycin and tetracycline. The major disadvantage of using topical antibiotics is bacterial resistance. They should not be used alone because combination with topical retinoids or benzoyl peroxide provides better results and reduce bacterial resistance.

Other topical treatments

Benzoyl peroxide is one of the most commonly-prescribed topical agents in mild to moderate acne. It may be used alone or in combination with topical or systemic antibiotics and retinoids. It has an antibacterial effect that comes from oxidation process in the skin. Localized dryness, erythema, and peeling of skin in the treated area may be seen. Azelaic acid has both antibacterial and keratolytic effects. It may be also be beneficial for postinflammatory hyperpigmentation because it can cause hypopigmentation.

ANDROGENIC ALOPECIA

Androgenic alopecia, also known as female-pattern hair loss, is a progressive non-scarring pattern loss of scalp terminal hair. In a normal hair cycle, the anagen phase (growth phase) is longer than the telogen phase (shedding phase), which produces long pigmented terminal hairs. However, in androgenic alopecia, the duration of anagen phase progressively decreases with each successive cycle, while the duration of the telogen phase remains constant, with an overall result of shorter and finer hair. Although androgenic alopecia is generally known as a hyperandrogenic cutaneous manifestation of PCOS, only a few reports have specifically examined androgenic alopecia in women with PCOS. The prevalence of PCOS in women with androgenic alopecia was reported to be in the range of 22-34.8% (70, 71). The main symptom in women is the patterned hair loss over the crown area with preservation of the frontal hair line; however, thinning and widening of the central part of the scalp and thinning associated with bi-temporal recession may be seen. Androgenic alopecia is related to significant psychological distress, negative effect on the quality of life, and serious impact on self-esteem. Diagnosis of androgenic alopecia is mainly clinical. The Ludwig scale and Sinclair scale have been used in clinical grading of female-pattern hair loss. There are conflicting results in the literature where some but not all studies have reported higher levels of serum androgens in women with androgenic alopecia (72, 73).

Treatment

Treatment is mainly focused on handling the underlying hormonal irregularities by using oral contraceptives with antiandrogenic activity and addition of supportive topical therapy with minoxidil solutions. Before starting therapy, all patients should be counseled about the duration of therapy and the importance of adherence to maintenance therapy.

Minoxidil

Minoxidil has a specific effect on the proliferation and differentiation of follicular keratinocytes that leads to prolongation of the anagen phase (74). Minoxidil is available in two forms; as 2% solution and 5% solution. The 5% solution showed no greater benefit compared with the 2% solution; however, there were more adverse effects with the 5% solution (75). It has few local adverse effects such as hypertrichosis, local irritation, and contact dermatitis.

Anti-androgens

Current options include combined oral contraceptives with low androgen effects and other specific anti-androgen therapies such as spironolactone and cyproterone acetate.

Spironolactone is an anti-androgen that shows anti-androgenic activity by decreasing production and blocking the effects of androgens at target tissue due to its competitive inhibitory activity on androgen receptor. The usual starting dosage is 100-200 mg/day. A study that compared efficacy of spironolactone and cyproterone acetate on androgenic alopecia found no significant difference between the two compounds; however, when both results were combined, 44% of women taking either spironolactone and cyproterone acetate had hair regrowth, 44% had no change (76).

Cyproterone acetate acts as an androgen receptor blocker with strong progestational activity. Cyproterone acetate has shown a beneficial effect in its use in the treatment of androgenic alopecia. It has no significant effect on hair regrowth but it has been shown to reduce hair shedding (77).

5 -alpha reductase inhibitors

Finasteride is a 5α-reductase type II inhibitor. In postmenopausal women with androgenic alopecia over a one-year period, administration of oral finasteride in a dosage of 1 mg daily had no superior effect when compared with placebo on hair growth or progression of hair loss (78). However, finasteride at a 5mg/week-doseage may be efficacious in the therapy of postmenopausal women with androgenic alopecia (79).

Dutasteride is a combined inhibitor of 5α-reductase type I and type II. Dutasteride was reported to be effective in a woman who had previously shown minimal improvement after 6 months of finasteride therapy (80).

Conclusion

Cutaneous manifestations of hyperandrogenism include hirsutism, acne and androgenic alopecia and are commonly observed in women with PCOS. Acne and hirsutism are

treated effectively with similar drug therapies. Combined oral contraceptives should be first-line agents for therapy of hirsutism and acne in women who also need contraception. Antiandrogens alone or in combination with combined oral contraceptives can be used in the treatment of hirsutism, acne and androgenic alopecia. To date, many studies reported the effects of therapeutic interventions in women without PCOS hence randomized controlled trials are required to make conclusions on treatment of hyperandrogenism in PCOS.

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