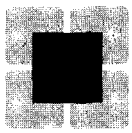

Treatment of androgenic disorders in women: acne, hirsutism, and alopecia

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■ Androgen excess disorders—acne, alopecia, and hirsutism—can be treated effectively with endocrine therapy such as androgen receptor blockers or antagonists, or with androgen suppression. Spironolactone, estrogen, and dexamethasone are considered the most effective approaches to treatment. Whatever the modality, careful planning is key to success, with recognition that response rates vary from patient to patient. A treatment regimen generally continues for at least 2 years.

□ INDEX TERM: ANDROGENS □ CLEVE CLIN J MED 1990; 57:428–432

HIRSUTISM AND ALOPECIA caused by androgen excess are considered difficult to treat, and they are often dismissed as variants of normal. However, women with androgen-associated hirsutism, alopecia, or the more manageable acne who are treated successfully are among the most grateful of patients, as well as the most compliant with physician recommendations.

Effective treatment is available for androgenic disorders, but the underlying endocrine disturbance varies from patient to patient and must be considered when planning treatment.[1-5] Treatment that is effective for one group may not be successful for another. Therefore, it is important, when caring for these patients, to establish realistic therapeutic expectations, particularly with regard to treatment time and response.

This article will delineate the treatment options for managing these common manifestations of androgen excess, and review the rationale for each modality.

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TREATMENT SELECTION

Three treatment options are available for the endocrine, or systemic, management of cutaneous signs of androgen excess: androgen receptor blockade, androgen antagonism, and suppression of adrenal or ovarian androgen production (*Table 1*). Because the mechanisms of androgen blockade and antagonism overlap, medications in these two categories are generally considered together.

Whether to select an endocrine modality *v* a nonendocrine, or topical, treatment depends on the nature of the abnormality, the patient's general health, and the possibility of adverse effects.[1] For example, a 40-year-old woman who smokes two packs of cigarettes daily is not a candidate for oral contraceptives. This treatment might decrease her serum testosterone, but the increased risk of cardiovascular disease and thrombophlebitis outweighs the potential benefits.

Patients who have elevated blood or urine androgen levels are best treated with a combination of receptor blockade and suppression of androgen production. The modality for suppression will differ depending on whether the site of production is ovarian or adrenal.

A variety of treatments that do not act on the endocrine system are useful nevertheless—for example,

TABLE 1
ENDOCRINE TREATMENT REGIMENS FOR ANDROGEN-EXCESS DISORDERS

Agent	Recommended dosage	Biological effect	Comments
Spironolactone (Aldactone)	75–100 mg/d in two divided doses	Androgen receptor blockade, some androgen antagonist activity	Side effects can be minimized with adequate hydration; dosages ≥200 mg/d associated with polymenorrhea
Cimetidine (Tagamet)	Up to 800 mg tid	Androgen receptor blockade	High doses needed for effect; few side effects
Dexamethasone	½ of 0.25-mg tablet hs to start; increase after 4 mo if necessary to 0.25 mg hs	Adrenal androgen suppression	With proper use, virtually free of side effects; may restore ovulation
Oral contraception (Demulen 1/35-21 or 1/35-28; Modicon 21 or 28; Brevicon 21- or 28-day Tablets; Ortho-Novum 7/7/7)		Ovarian androgen suppression	High-progesterone pills recommended for ovarian suppression alone; low-progesterone pills suitable for contraception or cyclic control
Leuprolide acetate (Lupron)	1 mg/d, SC	Ovarian androgen suppression	Useful when oral contraception not indicated, but best reserved for extreme conditions because of expense and need for SC administration
Conjugated estrogen (Premarin)	1.25 mg/d	Estrogen replacement	Higher doses than recommended for prevention of osteoporosis; needed to treat alopecia in menopause
Micronized estradiol (Estrace)	2 mg/d	Estrogen replacement	Higher doses than recommended for prevention of osteoporosis; needed to treat alopecia in menopause

acne therapies such as antibiotics, isotretinoin (Accutane), and topical retinoids. The best treatment of hirsutism is symptomatic, and includes electrolysis, plucking, shaving, and the use of depilatories. Treatment of alopecia includes topical and oral anti-androgens and topical hair promoters such as minoxidil.

ANDROGEN BLOCKADE AND ANTAGONISM

Increased pilosebaceous or target tissue sensitivity to androgens is thought to be the major factor in the pathogenesis of most androgen excess conditions. Therefore, androgen blockade is nearly always necessary to achieve a good therapeutic result.

Typically, the androgen receptor blockade drugs have been introduced for other indications and the androgen-blocking properties recognized only later. In male patients, these drugs cause undesirable effects such as gynecomastia or decreased potency.

Future drugs that can be classified specifically as androgen antagonists will probably be introduced first for the treatment of prostatic cancer and be studied later for their safety and efficacy in the treatment of androgen excess conditions. These new drugs may have more potent receptor blocking activity and more selectivity than drugs currently being used.

Thalidomide is one of several such drugs under investigation. The antifungal agent ketoconazole has androgen antagonist properties, but the hepatic toxicity associated with the systemic form of the drug makes it inappropriate for the treatment of androgen excess disorders. The topical form is useful in the treatment of seborrheic dermatitis to reduce *Pityrosporon* infections.

Inhibition of 5-alpha reductase, the enzyme that converts testosterone to its active form, dehydrotestosterone,[6] is another promising approach to treatment.

In the United States, the most effective androgen receptor blocker available is spironolactone (Aldactone).[7–10] Cimetidine and cyproterone acetate also have androgen receptor blockade activity.

Spironolactone

Spironolactone is the agent of choice in most androgen excess situations. Patients generally start therapy with a daily dosage of 75 mg to 100 mg, in two doses taken at breakfast and dinner. If the total dosage cannot be divided evenly, then the larger one is taken in the morning to minimize night-time diuresis.

Although higher dosages are more effective, they are also more likely to cause side effects. These can be minimized if the patient maintains hydration by drinking increased amounts of water. With proper hydration, hyper-

kalemia has been an insignificant problem in our experience. Spironolactone should be used with caution in patients with renal impairment or other factors that might be expected to produce hyperkalemia, and these patients should be monitored closely.

Rarely, spironolactone causes orthostatic dizziness and other symptoms of decreased plasma volume. Fatigue or lethargy is occasionally reported. The orthostatic symptoms and dizziness can be exacerbated by combining spironolactone and beta blockers for migraines or palpitations. This should be avoided if possible.

The most troublesome adverse effect of spironolactone is altered menstrual cycling. Typically, menstrual bleeding is increased slightly in amount, duration, and frequency. It is not unusual to have two prolonged menstrual periods a month. This can be corrected by reducing the spironolactone dosage or adding estrogen therapy. Polymenorrhea is associated with daily spironolactone dosages of 200 mg, and less often with lower dosages. Menstrual irregularities frequently resolve within 2 or 3 months of starting spironolactone therapy.

The etiology of the abnormal uterine bleeding is unknown. Possibly, spironolactone has estrogenic action on the uterus, especially since in men it tends to induce gynecomastia and in females mastodynia. The patient should be advised of these possible effects and they should be addressed if they arise.

The usual duration of spironolactone therapy is 1 to 2 years, after which intermittent therapy is given to the patient as needed.

Women who are taking spironolactone should be advised to use an effective method of birth control. There is concern about incomplete virilization of the genitalia of male infants born to women who take androgen antagonists during pregnancy, although this has not occurred in women receiving spironolactone.

Absorption of oral spironolactone may be erratic. Proper tablet manufacture will ensure that most of the active agent actually reaches the bloodstream. For this reason, there is reluctance to use generic substitutions of spironolactone.

Cimetidine

Cimetidine (Tagamet) also has androgen receptor-blocking activity. Controlled studies have demonstrated that cimetidine has some efficacy in the treatment of hirsutism,[11] but it seems to be less effective than spironolactone. Quite high doses of cimetidine are probably needed to achieve a good result. On the other hand, even at a dosage of 800 mg tid, cimetidine apparently has fewer adverse effects than spironolactone.

Cyproterone acetate

Cyproterone acetate is a potent progesterone with substantial androgen antagonist activity.[12,13] The drug is effective for the treatment of hirsutism, acne, and alopecia, even in some patients who do not respond to spironolactone. Usually, a 50- or 100-mg cyproterone dose is combined with 50 µg of ethylene estinol; the effect of the regimen on the patient is equivalent to that of a high-progesterone birth control pill.

Depression and, in some women, weight gain, are possible side effects. Cyproterone is unlikely to be available in the United States in the near future.

ANDROGEN SUPPRESSION

When blood androgen levels are elevated, androgen blockade alone may not achieve adequate therapeutic results. For example, spironolactone fails to achieve a satisfactory response in many women because their hyperandrogenemia remains uncorrected.

Suppressive therapy alone also will be ineffective unless the choice of adrenal *v* ovarian suppression is made correctly. This is the purpose of dexamethasone suppression testing.[1] If dexamethasone suppresses testosterone to 45 ng/dL or less, or androstenedione to 250 ng/dL or less, then it can be used for long-term suppression. Though suppression by dexamethasone does not establish the adrenal gland as the source of androgen, it does establish that dexamethasone will lower the serum androgen level. When dexamethasone suppression is only 40% to 50%, then the ovary is the likely source and oral contraception or another means of ovarian suppression would be the rational choice.

Dexamethasone

Dexamethasone is a potent drug with potentially catastrophic adverse effects. Accordingly, the agent must be used with extreme care and close monitoring. When used properly, dexamethasone is virtually free of adverse effects. Like other glucocorticoids, dexamethasone can produce skin atrophy with telangiectasias and striae. Weight gain, hypertension, adrenal suppression, and possible precipitation of diabetes mellitus also are possible effects.

To ensure safety when using dexamethasone, the dosage should be titrated to partial, rather than total, suppression of the adrenal gland.[14] The drug is best given at bedtime so that biologically effective levels will be present during the early morning hours when ACTH secretion is most active. We start therapy with one half of a 0.25-mg tablet at bedtime; the dosage may

be increased to the full 0.25-mg tablet if suppression is not achieved within 4 months. Dexamethasone has no appreciable irritant effect on the gastric mucosa and need not be taken with food.

In our experience, a daily dosage of 0.125 mg achieved suppression in 25% of women, 0.25 achieved suppression in 50%, and all others were suppressed on 0.375 mg.[15] Weight gain was not observed, even after many months of dexamethasone therapy, but one or two women on the 0.375-mg dosage appeared to have Cushingoid facies. Because adrenal suppression is only partial, the ability to respond to stress seems to be preserved.

Dexamethasone restores ovulation in some patients who have been anovulatory secondary to androgen excess. Modest doses appear to be safe during pregnancy; in fact, women who are attempting pregnancy are advised to continue the dexamethasone until pregnancy is confirmed and then discontinue the drug.

Oral contraception

When dexamethasone does not suppress androgen production, then the ovary is the probable source of the androgen and oral contraceptives have a role in treatment.

Many factors influence the choice of birth control pill.[16,17] Most synthetic progesterones have some degree of androgenic activity, which is undesirable in patients who already have signs of androgen excess. Pills containing norgestrel and levonorgestrel are therefore not the first choice for patients with androgen excess.

Oral contraceptives that appear to be useful in androgenic disorders include Demulen 1/35-21 or 1/35-28 (35 μg ethinyl estradiol, 1 mg ethynodiol diacetate); Ovcon 35 (35 μg ethinyl estradiol, 0.4 mg norethindrone); Modicon 21 or 28 or Brevicon 21- or 28-Day Tablets (35 μg ethinyl estradiol, 0.5 mg norethindrone); Ortho-Novum 7/7/7 (ethinyl estradiol and norethindrone). The progesterone ethynodiol diacetate is a relatively low androgenic progesterone. Norethindrone is more androgenic, but the low doses contained in Ovcon-35, Modicon, and Brevicon make these pills relatively nonandrogenic.

High-progesterone pills are recommended when ovarian suppression is the goal; low-progesterone pills, such as Demulen, are appropriate when contraception or cyclic control is the primary objective. Because the low-dose pill is safer, estrogen doses in excess of 50 μg should be used only when a 35-μg dose has proved unsatisfactory.

Oral contraception alone is frequently ineffective for the treatment of hirsutism unless the elevated androgens are of ovarian origin.

Leuprolide acetate

Leuprolide acetate (Lupron), an analog of gonadotropin-releasing hormone, effectively lowers ovarian androgen secretion,[18] and is particularly useful in older women or others who are not candidates for oral contraceptive therapy. The usual recommended dose, 1 mg subcutaneously per day, reduces ovarian androgen secretion by half. A 2-mg dose lowers the secretion nearly to prepubertal values. However, the agent is expensive. That, the need for daily injections, and the resulting estrogen deficiency all limit its usefulness. It is best reserved for extreme conditions. A depot form will be available shortly and may have a wider application, but indications and the proper mode of use have yet to be defined.

Menopausal estrogen replacement

It is not unusual for alopecia and, less frequently, acne and hirsutism, to develop in the perimenopausal female. These women usually have low androgen levels. Since estrogen replacement therapy is indicated during menopause for other reasons, it is usually appropriate to prescribe it for alopecia. The dosage needed to preserve hair is higher than that currently recommended for protection against osteoporosis. A daily dose of conjugated estrogen (Premarin), 1.25 mg, or micronized estradiol (Estrace), 2 mg, is necessary to have a positive effect on scalp hair. With appropriate progestin supplementation to protect against endometrial carcinoma, this regimen is usually sufficient for alopecia.

If androgens are elevated, then spironolactone or occasionally dexamethasone may be appropriate adjunctive therapy. Very high androgen levels or virilization in this group should prompt a search for an adrenal or ovarian tumor.

FOLLOW-UP

Treatment of androgen excess disorders generally lasts at least 2 years, and its success depends on a considerable investment of time by both physician and patient. Most such patients are followed at 4-month intervals for symptomatic improvement and laboratory assessment of the efficacy of drug therapy.

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