



Complete Summary

GUIDELINE TITLE

AACE medical guidelines for clinical practice for the diagnosis and treatment of hyperandrogenic disorders.

BIBLIOGRAPHIC SOURCE(S)

AACE medical guidelines for clinical practice for the diagnosis and treatment of hyperandrogenic disorders. Endocr Pract 2001 Mar; 7(2):120-134. [86 references]

COMPLETE SUMMARY CONTENT

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METHODOLOGY - including Rating Scheme and Cost Analysis

RECOMMENDATIONS

EVIDENCE SUPPORTING THE RECOMMENDATIONS

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

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IMPLEMENTATION OF THE GUIDELINE

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT

CATEGORIES

IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

Hyperandrogenic disorders, including the following clinical manifestations:

- Disorders of the pilosebaceous unit
 - Acne
 - Hirsutism
 - Alopecia
 - Virilization
- Ovulatory dysfunction
 - Amenorrhea
 - Infertility

GUIDELINE CATEGORY

Diagnosis
Evaluation

Management
Treatment

CLINICAL SPECIALTY

Dermatology
Endocrinology
Family Practice
Internal Medicine
Obstetrics and Gynecology
Pediatrics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide guidelines for the diagnosis and treatment of hyperandrogenic disorders in women

TARGET POPULATION

Women with suspected or confirmed hyperandrogenic disorders

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Patient and family history, including patient age at thelarche, adrenarche, and menarche; reproductive history
2. Physical examination, including vital signs, pelvic examination and/or pelvic ultrasonography; determination of body mass index and waist-to-hip ratio; evaluation of degree of hirsutism (Ferriman-Gallwey Scale), alopecia, and acne; evaluation for acanthosis nigricans
3. Measurement of plasma hormone levels, including total and free testosterone, dehydroepiandrosterone sulfate (DHEAS), prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and 17-hydroxyprogesterone
4. Adrenal suppression tests, such as 2-, 4-, or 6-day dexamethasone suppression tests
5. Cosyntropin stimulation test
6. Gonadotropin-releasing-hormone (GnRH) stimulation test
7. Evaluation of ovulation through basal body temperature chart and serum progesterone levels
8. Measurements of fasting morning glucose and insulin or glucose tolerance tests
9. Measurement of blood lipids and triglycerides

Treatment/Management

Pharmacologic therapy

1. Glucocorticoids, such as prednisone or dexamethasone
2. Oral contraceptives, including third-generation oral contraceptives containing desogestrel and norgestimate
3. Antiandrogens, such as spironolactone, cyproterone acetate, flutamide.
(Note: cimetidine and ketoconazole are considered but not recommended.)
4. 5 alpha-reductase inhibitors, such as finasteride
5. Insulin-sensitizing agents, such as metformin and thiazolidinediones
6. Gonadotropin-releasing hormone (GnRH) agonists
7. Bromocriptine or cabergoline

Nonpharmacologic therapy

1. Weight reduction
2. Surgical excision of a virilizing adrenal or ovarian tumor
3. Electrocautery in patients with polycystic ovary syndrome

MAJOR OUTCOMES CONSIDERED

- Androgen levels
- Degree of ovarian dysfunction
- Occurrence of metabolic or cardiovascular consequences of hyperandrogenism, such as diabetes mellitus, hypertension, dyslipidemia or atherosclerosis
- Degree and distribution of acne, hirsutism, and alopecia

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Not stated

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Nine physicians are acknowledged as reviewers in the guideline document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Diagnostic Evaluation of Hyperandrogenism

In most cases, the symptoms usually associated with hyperandrogenism (hirsutism, menstrual dysfunction, and infertility) are not brought to the attention of a physician for evaluation until the patient is in her late teens, early 20s, or later. Clearly, the most common causes of hyperandrogenism begin in early adolescence; therefore, every attempt should be made to diagnose and treat these conditions as early as possible. The diagnostic responsibility lies with the primary-care physicians, pediatricians, and gynecologists, particularly those who deal with "adolescent gynecology", who first come in contact with these young patients.

The diagnostic evaluation is designed to provide information about the specific androgens involved (for example, testosterone, free testosterone, and dehydroepiandrosterone sulfate [DHEAS]), the degree of hypersecretion, the organs of origin of the androgen excess (such as the ovaries or adrenal glands), and the pathogenesis of the excess androgen production. Furthermore, the evaluation must determine whether the excessive production of the androgens is due to organ dysfunction, hyperplasia, or a neoplasm. In addition, the degree of

the effect of the hyperandrogenism on the integument, reproductive system, cardiovascular system, and metabolic function should be determined.

History and Physical Examination

A thorough history and physical examination provide the most important initial diagnostic information, whereas laboratory tests should usually serve to confirm the presence of hyperandrogenemia. The history should include information about the patient's age at thelarche, adrenarche, and menarche. If obesity is present, the time of onset and the progression should be noted. The character of the menstrual cycles (their frequency, duration, and occurrence of dysmenorrhea) along with the reproductive history, including miscarriages, should be evaluated. The patient should be questioned about the age at onset and the progression of the following factors: hirsutism, acne, excessive sebum, seborrhea, and alopecia. One should also note medications used and their effects on acne and hirsutism. The family history is important in determining whether other family members have hirsutism, acne, infertility, diabetes mellitus, cardiovascular disease, dyslipidemia, or obesity. The presence of premature balding (<35 years old) in male siblings of women with hyperandrogenism has been described.

A complete physical examination including pelvic examination or pelvic ultrasonography (or both) is required. In addition to the usual vital signs, the measurements of height, weight, and waist circumference and the determination of the body mass index and the waist-to-hip ratio (WHR) are essential. The waist-to-hip ratio (normal women, <0.8) and body mass index are important in assessing the degree of obesity in women with hyperandrogenism. A longitudinal 4-year follow-up of 32,898 women who were 55 to 69 years of age and had an increased waist-to-hip ratio revealed a significantly increased risk of mortality attributable to coronary artery disease.

Particular attention should be paid to the degree and distribution of cutaneous manifestations of androgen excess (hirsutism, acne, and alopecia). The degree of hirsutism can best be documented and graded by using a system such as the one presented in Figure 1 and Table 1 in the original guideline document. In addition, the presence of clitoral hypertrophy and acanthosis nigricans (an epiphenomenon of brown and sometimes verrucous hyperpigmentation on the sides and back of the neck, axillae, submammary region, subpanniculus areas, perineum, or vulva) should be noted. Acanthosis nigricans as well as the presence of skin tags, usually in the neck area, may be indicators of insulin resistance. Examination of the thyroid gland and breasts (presence of galactorrhea) should be emphasized. A thorough pelvic examination should include an inspection of the vulva for the presence of clitoral hypertrophy and of the cervix for the state of dilatation of the cervical os and presence and type of cervical mucus. This last factor may be of considerable help in determining the patient's ovulatory status. The uterus should be examined for size and the presence of tumors. Similarly, the adnexae should be examined for the presence of masses. In the obese patient, pelvic examination can be imprecise and limited. Under these circumstances, pelvic ultrasonography is imperative for identifying pathologic changes in the pelvic organs.

Although a pelvic ultrasound study demonstrates typical subcortical ovarian cysts ranging from 5 to 10 mm and having an increased stroma in most women with polycystic ovary syndrome (PCOS), these morphologic findings are nonspecific

and may be found in other diseases or in normal women. Similar ultrasound patterns can be found in nonclassic adult-onset congenital adrenal hyperplasia (CAH), hyperprolactinemia, and thyroid dysfunction and in perimenarchal girls. Thus, the ultrasound picture of a polycystic ovary should not be used as a criterion for the diagnosis of polycystic ovary syndrome. Despite the nonspecificity of pelvic ultrasonography, it can reveal ovarian size, the nature of ovarian follicles and stroma, the state of the endometrium, the response to therapy, and the diagnosis of ovarian neoplasms (primarily dermoids).

Laboratory Studies

Although the evaluation of androgen levels and their site of secretion in patients with suspected hyperandrogenism is essential, other endocrine studies, particularly as suggested by the history and physical examination, are in order. The determination of luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, glucose, and lipid levels is of particular interest during the initial laboratory evaluation.

The laboratory evaluation of the patient with clinical signs of hyperandrogenism necessitates specific knowledge and assessment of the endocrine testing being performed. Special care must be exercised to select a laboratory known to the physician to be proficient in androgen determinations—that is, a laboratory that has made an effort to obtain appropriately timed blood samples and has reliably determined the "normal" or the "reference" ranges for the hormones tested. Many commercial laboratories do not provide accurate, sensitive, and reproducible hormone determinations, particularly for androgens. The most challenging problems are encountered with the determination of testosterone levels in normal female patients who have testosterone levels in the low range of assay detection. Many commercial laboratories have inaccurate normal ranges for testosterone levels, as evidenced by the fact that most research publications report much lower normal-range levels for women without hyperandrogenism than do commercial laboratories. Studies have shown that the same testosterone value measured by different laboratories may be designated as normal to abnormally high when compared with the supplied reference ranges. Thus, an acceptable clinical laboratory should provide precise results, a reliable reference range, and quality control that ensures stable values over extended periods. These features are crucial because long-term therapy for hyperandrogenism is frequently necessary.

During the initial assessment of a patient with suspected hyperandrogenism, the following plasma hormone concentrations could be determined during fasting in a specimen obtained during the first 7 days of the menstrual cycle: total and free testosterone, dehydroepiandrosterone sulfate (DHEAS), prolactin, luteinizing hormone and follicle-stimulating hormone, and 17-hydroxyprogesterone (17-OHP).

The determination of plasma free testosterone may help detect the presence of subtle hyperandrogenemia in some patients in whom the total testosterone level is normal. Of note, obese women may have a high free testosterone value because of reduced sex hormone-binding globulin (SHBG) attributable to hyperinsulinemia. A high dehydroepiandrosterone sulfate level may indicate an adrenal factor in androgen production and, if substantially elevated, the presence of an adrenocortical neoplasm. The usefulness of a high luteinizing hormone level

or an elevated luteinizing hormone/follicle-stimulating hormone ratio (>2.5) in diagnosing the presence of polycystic ovarian state in women with hyperandrogenism is limited, inasmuch as at least a third of the patients with polycystic ovary syndrome do not demonstrate this abnormality. In reference to reproductive function, however, a high luteinizing hormone level is associated with a poor response to attempted induction of ovulation and an increased risk of miscarriage.

Measurement of plasma 17-hydroxyprogesterone levels is useful in diagnosing adrenal hyperandrogenemia as a result of 21-hydroxylase deficiency. A high 17-hydroxyprogesterone level suggests the presence of this enzyme deficiency disease. With a suspicious family history of congenital adrenal hyperplasia or in Ashkenazi women, the use of a cosyntropin stimulation test may be necessary to exclude this enzyme deficiency.

Many clinicians have found that women with clinical signs of hyperandrogenism who undergo initial assessment after the age of 35 years may not demonstrate hyperandrogenemia. This finding may prevail because, with aging, the hyperandrogenic activity (particularly that of the ovaries) decreases and the hirsutism will persist. Therefore, follow-up monitoring of such women for the development of associated metabolic and cardiovascular sequelae is important.

Determination of Site of Androgen Production

The hypersecretion of androgens can be attributed to the ovaries, the adrenal glands, or the peripheral conversion of androgen precursors. From the standpoint of therapeutic strategy, determining the degree of contribution of the androgens originating from each site is critical. For this purpose, several endocrine function tests are available.

Adrenal Suppression Test

Two-Day Suppression Test

The following steps are involved in the 2-day dexamethasone suppression test.

Day 1

- Beginning at 8 to 9 AM, obtain three blood samples at 20-minute intervals. Equal aliquots of each sample are pooled to provide the baseline sample (before administration of dexamethasone).
- Dispense to the patient eight 0.5-mg dexamethasone tablets.
- The patient takes one tablet of dexamethasone at lunch, dinner, and bedtime.

Day 2

- The patient takes one tablet of dexamethasone at breakfast, lunch, dinner, and bedtime.

Day 3

- The patient takes one tablet of dexamethasone at breakfast.
- Subsequently, beginning within 2 hours, three blood samples are obtained every 20 minutes. Equal aliquots of each sample are pooled to provide the "postdexamethasone" sample.
- Testosterone, dehydroepiandrosterone sulfate, and cortisol are measured on pooled blood samples obtained before and after administration of dexamethasone.

Alternative Suppression Tests

Some authorities suggest the use of 4 to 6 days of suppression with dexamethasone. These tests are conducted in the same fashion as the 2-day suppression test. Some investigators believe that such tests yield no substantially greater amount of information than the 2-day dexamethasone suppression study.

Interpretations

If the high level of testosterone is suppressed more than 40% and dehydroepiandrosterone sulfate is suppressed more than 60% after administration of dexamethasone, the source of the increased androgen is most likely the adrenal glands.

If the testosterone level fails to be suppressed but dehydroepiandrosterone sulfate and cortisol respond, the source of testosterone is primarily the ovaries.

If testosterone suppression is less than 40%, a combined ovarian and adrenal contribution is responsible for the excessive testosterone secretion.

If lack of androgen suppression is associated with a lack of cortisol suppression, the patient most likely has adrenal hyperfunction (for example, Cushing's disorder or adrenal cancer) or the patient may have failed to take the dexamethasone tablets as directed. Appropriate steps must be taken to determine which of these two possibilities is the likely explanation.

Stimulation Tests

Adrenal Stimulation

The cosyntropin stimulation test is conducted for detection of the various steroidogenic enzyme deficiencies of the adrenal glands, predominantly 21-hydroxylase deficiency. This test is indicated only if a screening morning 17-hydroxyprogesterone level is above normal or the suspicion of such an enzymatic deficiency is high, as in Ashkenazi and Hispanic women. A morning plasma cortisol level and 17-hydroxyprogesterone level are determined, and 0.25 mg of cosyntropin is administered intravenously. Blood sampling is repeated at 60 minutes. Specific testing for other adrenocortical defects may also be performed to exclude the presence of 3 beta-ol dehydrogenase and 11 beta-hydroxylase deficiencies.

Ovarian Stimulation

The gonadotropin-releasing hormone (GnRH) stimulation test is conducted to confirm the ovarian origin of the excessive androgens. This test involves suppression of the adrenal glands with dexamethasone and, while the adrenal glands are suppressed, stimulation of the ovaries with a gonadotropin-releasing hormone agonist (for example, nafarelin). Blood samples are collected at various time intervals during a 25-hour period. The hypersecretion of 17-hydroxyprogesterone is the endpoint of the test, indicating ovarian involvement. This test is useful only in clinical research of polycystic ovary syndrome to identify the presence of 17-hydroxylase dysfunction.

Determination of Degree of Androgen-Induced Changes

Integument

The degree and distribution of acne and hirsutism, as well as alopecia when present, should be assessed with use of the Ferriman-Gallwey scoring technique (illustrated in Figure 1 and Table 1 of the original guideline document) or a similar scale.

Ovaries

Menstrual cycles can be defined as ovulatory or anovulatory. A simple method to evaluate ovulation is the use of a basal body temperature chart, in which a biphasic pattern suggests an ovulatory cycle, whereas a flat pattern is consistent with anovulation. A serum progesterone level of less than 2 ng/mL after the 21st day of the menstrual cycle or after a perceived increase in the basal body temperature is also consistent with ovulatory dysfunction.

Metabolic Sequelae

The metabolic sequelae of hyperandrogenemia are of major importance and need to be considered during the early assessment of patients with clinical signs of hyperandrogenism. The increased incidences of hyperinsulinism and insulin resistance make these patients susceptible to impaired glucose tolerance and, ultimately, overt type 2 diabetes mellitus. Although the "gold standard" for defining insulin resistance (other than a euglycemic-hyperinsulinemic clamp study) is the frequently sampled intravenous glucose tolerance test, fasting morning glucose and insulin measurements may be a useful screening test to determine the presence of these metabolic abnormalities. A ratio of fasting glucose/insulin <4.5 has been proposed as an indicator of insulin resistance in such patients. In a recently published study, reevaluation of this issue provided evidence that an effective method to determine the presence of insulin resistance is to measure the total integrated insulin response to orally administered glucose. The fasting insulin level correlated highly with this more elaborate testing.

In addition to impaired glucose metabolism, dyslipidemia characterized by reduced high-density lipoprotein cholesterol and increased triglyceride levels is frequently noted. These manifestations place patients with hyperandrogenism at an increased risk for later cardiovascular atherogenic complications. Although treatment of hyperandrogenism is important for the alleviation of the cutaneous (acne and hirsutism) or menstrual (ovulatory dysfunction) abnormalities, a major goal of treatment is possible amelioration of the metabolic disorders. The natural

history of the disease has not been studied in a sufficiently large series of patients with hyperandrogenism. On the basis of the available data, however, these patients are clearly at risk, and this factor should be at the forefront of therapeutic considerations.

Therapy for Hyperandrogenism

Although the therapeutic approach for hyperandrogenism is usually directed at the primary symptom of the patient—acne, hirsutism, alopecia, menstrual dysfunction, infertility, or an associated metabolic disorder—the primary concern is a thorough diagnostic evaluation to determine the degree of hyperandrogenism, the site of excess androgen production, and the presence of all pathophysiologic and metabolic manifestations. Early recognition of the disease process and timely therapeutic intervention should be of foremost concern. Frequently, the disease can be diagnosed in the perimenarchal or early postmenarchal period of the female patient's development. Early treatment may prevent serious problems with acne, hirsutism, dysfunctional bleeding, and infertility and possibly ameliorate the potential later development of metabolic and cardiovascular complications.

Therapy may be categorized on the basis of the results of dynamic tests and the pathophysiologic findings:

- Predominantly glucocorticoid-suppressible hyperandrogenism (probably adrenocortical in origin)
- Combined ovarian and adrenal hyperandrogenism
- Predominantly ovarian hyperandrogenism
- Rare forms of hyperandrogenism:
 - Congenital adrenal hyperplasia
 - Adrenal tumors
 - Ovarian tumors
 - Hyperthecosis

The pharmacologic options in the treatment of the aforementioned disorders include the following:

- Suppression of adrenal androgens (administration of glucocorticoids, usually in physiologic doses of dexamethasone or prednisone)
- Suppression of ovarian androgens (administration of female sex steroids, in the form of either birth control pills or estrogens and progestins, or administration of gonadotropin secretion blocking agent—that is, gonadotropin-releasing hormone agonists with 'add-back' estrogen therapy)
- Treatment with antiandrogens (for example, spironolactone and flutamide)
- Treatment with insulin-sensitizing agents (metformin and thiazolidinediones)
- Treatment with 5 alpha-reductase-inhibiting agents (finasteride)
- Bromocriptine

Of importance, treatment with antiandrogens, insulin-sensitizing agents, and 5 alpha-reductase-inhibiting agents is not specifically approved by the United States Food and Drug Administration and is contraindicated during pregnancy.

Nonpharmacologic interventions for hyperandrogenic states include the following: (1) weight reduction, (2) surgical excision of a virilizing adrenal or ovarian tumor, and (3) electrocautery in patients with polycystic ovary syndrome.

Treatment With Glucocorticoids

Adrenal hyperandrogenism responds well to glucocorticoid therapy with prednisone or dexamethasone. Usually, 5 to 7.5 mg of prednisone or 0.25 to 0.5 mg of dexamethasone is administered daily after supper for 2 or 3 months. This treatment frequently results in normalization of the androgens. If the androgen levels are normalized, the dose is lowered to 5 mg of prednisone or 0.25 mg of dexamethasone for 2 to 3 months, at which time the dose can be halved or totally discontinued. The androgen levels should then be assessed every 3 to 4 months for 1 year for recurrence of hyperandrogenemia. Of note, the possibility of recurrence of high testosterone levels is greater than recurrence of high dehydroepiandrosterone sulfate levels. In most instances, dehydroepiandrosterone sulfate levels remain suppressed indefinitely after treatment. Suppression of androgens usually results in sustained amelioration of acne and has a minor effect on hirsutism (slowing of growth rate and softening of hair). Improvement in ovulatory activity, return of fertility, and increased sensitivity to the effect of clomiphene citrate on induction of ovulation often occur with glucocorticoid therapy.

The long-term adverse effects of minimal-dose glucocorticoid therapy on bone resorption and dysmetabolic syndrome have not been scientifically studied. Routine follow-up studies of patients have not shown significant effects on glucose or lipid metabolism; however, short-acting corticosteroids, such as prednisone, would be less likely to pose such risks in comparison with the use of dexamethasone.

Treatment With Oral Contraceptives

Oral contraceptives (OCs) are used widely for treatment of hyperandrogenism. The use of third-generation oral contraceptives in the treatment of ovarian hyperandrogenism appears promising in that little if any androgenic effect has been noted with desogestrel and norgestimate, the progestins used in these oral contraceptive agents. Acne and mild hirsutism are often decreased. The combination of oral contraceptives and antiandrogenic agents, particularly spironolactone, is often used in patients with moderate to severe hirsutism or alopecia. A major benefit is the reduction in the incidence of endometrial and ovarian cancer in patients who use oral contraceptives. Contraindications to their use may be a history of phlebitis, severe migraine, substantial weight gain, and the risk of increased insulin resistance. Long-term use may mask severe ovulatory dysfunction, which may progress to anovulation and amenorrheic states that are more resistant to induction of ovulation.

Treatment With Antiandrogens

Spironolactone

Spironolactone is an antiandrogen that competes with testosterone and dihydrotestosterone at the androgen receptor level. The minimal dose should be

100 mg daily in divided dosage and may be increased to 200 mg daily as tolerated. The combination of spironolactone and oral contraceptives is frequently used. The luteinizing hormone suppressive effect of oral contraceptive makes this combination treatment more effective than spironolactone monotherapy. This combined drug strategy minimizes the frequently noted polymenorrhea when spironolactone is used alone. Some of the side effects include light-headedness, fatigue, mood swings, reduced libido, headaches, and mastalgia. In patients with androgenetic alopecia, the use of spironolactone is effective in improving the rate of hair regrowth and preventing further scalp hair loss.

Cyproterone Acetate

Cyproterone acetate has not been approved by the United States Food and Drug Administration. Reports indicate that this progestational antiandrogen is effective in the treatment of hyperandrogenism. When administered in conjunction with ethinyl estradiol, it is equal or perhaps slightly superior to combination therapy with spironolactone and oral contraceptives.

Flutamide

Flutamide, an antiandrogen that blocks androgen uptake and nuclear binding, is a very effective drug in treating hyperandrogenism, but it has the potential, albeit infrequent, adverse effect of fatal hepatotoxicity. Flutamide should be used cautiously only in the most severe cases resistant to other forms of treatment. Recent data indicate that a dosage of 250 mg daily may be as effective as 250 mg twice a day.

Cimetidine

An H₂ blocker, cimetidine has not been found to be useful in the treatment of hyperandrogenism and is not recommended in this setting.

Ketoconazole

Ketoconazole is an antifungal agent that has shown some effectiveness in treating symptoms of androgen excess. Reports of serious hepatotoxicity, however, have made this drug treatment of questionable value.

Treatment With 5Alpha-Reductase Inhibitors

Finasteride is a 5alpha-reductase inhibitor that blocks the intracellular conversion of testosterone to dihydrotestosterone; thus, the amount of dihydrotestosterone available for interacting with the androgen receptor is reduced. Finasteride has a predominant effect on the type 2 isoenzyme of 5alpha-reductase that specifically affects sebaceous gland activity. Reports of its use in women have been limited to those with hirsutism, and it seems to be comparable to spironolactone in reducing anagen hair shaft diameter when administered in a daily dose of 5 to 7.5 mg. It is associated with minimal gastrointestinal side effects, and it does not alter menstrual cyclicality. The plasma levels of testosterone may increase during treatment, whereas the dihydrotestosterone level decreases. Of utmost importance, the patient should be aware that she must avoid pregnancy during

treatment with finasteride because of the potential for causing ambiguous genitalia in a male fetus.

Treatment With Insulin-Sensitizing Agents

The advent of drugs that enhance insulin sensitivity and action makes agents such as metformin and the thiazolidinediones important in the therapeutic strategy for patients with hyperandrogenism and some of the associated metabolic disturbances—specifically, insulin resistance. Studies have indicated that reducing plasma insulin levels substantially ameliorates the hyperandrogenism of polycystic ovary syndrome. Insulin-sensitizing agents may become a choice for initial treatment of women with hyperandrogenism, particularly those with polycystic ovary syndrome and insulin resistance, obesity, and moderate to severe oligomenorrhea.

Metformin

Reduction in the manifestations of hyperandrogenism and improved menstrual function have been reported with administration of metformin. Metformin has been administered in conjunction with ovulation-inducing agents, such as clomiphene citrate, and has not been reported to be teratogenic.

Many studies have demonstrated the most dramatic reduction in hyperandrogenism in obese subjects with polycystic ovary syndrome; hence, the issue has been raised whether weight reduction alone accounts for this effect. Questions have been posed about the reported efficacy of metformin in increasing insulin sensitivity in this type of patient because of the small numbers of subjects and questionable study designs in most reports dealing with this issue. Recently, however, a carefully designed study suggested a definite positive effect of metformin in a relatively large population of patients.

The recommended dosage of metformin for treatment of hyperandrogenic states is the initiation of therapy with 850 mg (one tablet) in the morning with breakfast, and then increasing the dosage to 1,700 mg after 2 to 3 weeks in divided doses with breakfast and dinner. Alternatively, metformin therapy can be initiated at 500 mg with dinner and increased to 500 mg twice and three times daily or to 1,000 mg twice a day as tolerated. The most common side effects are gastrointestinal; they consist of bloating, nausea, vomiting, and diarrhea and frequently occur during initiation of treatment. The occurrence of lactic acidosis is extremely rare and is more likely in those patients with renal impairment. Use of metformin should be discontinued before administration of contrast dye, particularly in subjects with decreased renal function.

Thiazolidinediones

Thiazolidinediones have been used alone or in combination in the treatment of type 2 diabetes mellitus. The primary effect of these drugs is achieved by improving insulin sensitivity in muscle and adipose tissue, as well as inhibiting hepatic gluconeogenesis. The decrease in insulin resistance is accompanied by a reduction in hyperinsulinemia, without associated weight changes. Studies have indicated that the use of troglitazone improved insulin sensitivity and subsequently decreased insulin-mediated ovarian androgen excess in women with

polycystic ovary syndrome, even in those subjects with severe obesity. In view of the occasional reports of serious hepatic disturbances associated with its use, however, troglitazone was removed from the market. Other agents in the thiazolidinedione class of drugs may prove to be effective in the treatment of polycystic ovary syndrome, but to date, no scientific studies have been published of their use in polycystic ovary syndrome.

Comment

Overall, the use of insulin-sensitizing agents has demonstrated clinical improvement in hirsutism and menstrual cyclicity. Improvement in responsiveness to ovulation-inducing agents (specifically, clomiphene citrate) has been reported. The effects on improvement of the cutaneous manifestations of hyperandrogenism may not be as pronounced as those achieved with antiandrogen treatment in combination with oral contraceptives.

Further studies are needed to determine the exact role of metformin and thiazolidinediones as therapeutic agents, or possibly initial monotherapy, in the treatment of hyperandrogenic states, including polycystic ovary syndrome.

Treatment With Gonadotropin-Releasing Hormone (GnRH) Agonists

The use of gonadotropin-releasing hormone agonists is most effective in severe forms of ovarian hyperandrogenism. Depot preparations of gonadotropin-releasing hormone agonists may be administered at monthly intervals. Because of the severe hypoestrogenemia induced by gonadotropin-releasing hormone agonists, however, a concurrent add-back therapy with estrogen and progesterone (the latter when the uterus is present) is essential. This therapy will also correct the severe vasomotor symptoms and other side effects of the resulting hypoestrogenemia. Gonadotropin-releasing hormone agonists have shown no effect in reducing hyperinsulinism in instances of ovarian hyperandrogenism.

Treatment With Bromocriptine

The use of bromocriptine, a dopamine receptor agonist, in a divided dosage of 5 to 7.5 mg daily with meals is indicated in the subset of women with hyperandrogenism who have hyperprolactinemia. No convincing data indicate that this treatment is effective in women with hyperandrogenism who do not have high levels of circulating prolactin. Bromocriptine improves menstrual cyclicity in patients with hyperprolactinemia who have polycystic ovary syndrome and may reduce some of the associated hirsutism, which is related to augmented production of adrenal androgen attributable to the hyperprolactinemia. Treatment with bromocriptine should be initiated gradually so as to minimize initial light-headedness, hypotension, and nausea (vaginal or rectal administration can also reduce symptoms). Alternatively, use of cabergoline in dosages of 0.5 mg weekly or twice weekly may be associated with fewer side effects.

Weight Reduction

Obesity is present in 55 to 65% of patients with polycystic ovary syndrome, the most common form of hyperandrogenism, and is associated with an increase in

the waist-to-hip ratio and a history of perimenarchal onset. Obesity is frequently associated with insulin resistance and hyperinsulinism, which act synergistically with luteinizing hormone to intensify ovarian hyperandrogenism, decrease hepatic production of sex hormone-binding globulin (SHBG), and reduce insulin-like growth factor binding protein-1. Moreover, obesity reinforces the genetic predisposition to hormonal and ovulatory disorders in polycystic ovary syndrome. Metabolic complications are more common in obese patients with polycystic ovary syndrome (impaired glucose tolerance in approximately 40% of subjects with obesity, hypertension, dyslipidemias, and possible development of estrogen-dependent tumors) than in lean women with polycystic ovary syndrome.

Weight loss in patients with hyperandrogenism, with or without the clinical presence of polycystic ovary syndrome, should be the first therapeutic option because it decreases androgen levels, increases sex hormone-binding globulin, and may restore ovulation. As little as a 7% reduction in body weight can restore fertility, decrease hirsutism in some women with androgen excess, and improve the response to induction of ovulation. Investigators have also demonstrated that abnormalities in 17,20-lyase activity diminish in parallel with reduction of hyperinsulinemia.

Individualization of Therapy

The choice of therapeutic intervention for hyperandrogenism depends on several factors:

- The source of the hyperandrogenism
- The goal of therapy
- The long-term risks and benefits

The evaluation and treatment of hyperandrogenism and hyperandrogenemia should begin as early as possible after the onset of symptoms. Often, mild symptoms, such as menstrual irregularities, hirsutism, and acne, are overlooked or discounted, and the result is their progression. For example, adolescent patients diagnosed with a hyperandrogenic disorder should undergo assessment for treatment based on the cause of the hyperandrogenism, the long-term goals, and the potential benefits and risks.

For those patients with glucocorticoid-suppressible hyperandrogenism, successful treatment for 1 to 2 years may yield a long-term remission and prevent metabolic and ovulatory disorders.

In non-glucocorticoid-suppressible hyperandrogenism, the use of an oral contraceptive-antiandrogen combination may be effective in treating the hyperandrogenemia but may not ameliorate the long-term metabolic and ovulatory abnormalities. Therefore, patients should be counseled that discontinuation of therapy may lead to recurrence of the hyperandrogenic problems.

Insulin-sensitizing drugs have been shown to be effective in short-term studies, but long-term outcomes are as yet unknown. Those patients, regardless of age, with severe forms of polycystic ovary syndrome, such as those with insulin

resistance, obesity, and acanthosis nigricans, are candidates for this therapeutic modality.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Early recognition of the disease process and timely therapeutic intervention
- Early treatment may prevent serious problems with acne, hirsutism, dysfunctional bleeding, and infertility, and possibly ameliorate the potential development of metabolic and cardiovascular complications

Subgroups Most Likely to Benefit:

Adolescent patients, because the most common causes of hyperandrogenism begin in early adolescence

POTENTIAL HARMS

- Long-term use of oral contraceptives for treatment may mask severe ovulatory dysfunction, which may progress to anovulation and amenorrheic states that are more resistant to induction of ovulation.
- Treatment with antiandrogens can produce such side effects as light-headedness, fatigue, mood swings, reduced libido, headaches, and mastalgia.
- Treatment with metformin has been associated with gastrointestinal side effects (bloating, nausea, vomiting, and diarrhea), which frequently occur during initiation of treatment. Lactic acidosis occurs rarely.
- Treatment with troglitazone has been linked with serious hepatic disturbances; however, this drug has been removed from the market.
- Treatment with bromocriptine can cause light-headedness, hypotension, and nausea.
- Treatment with spironolactone can provoke polymenorrhea. Other side effects include light-headedness, fatigue, mood swings, reduced libido, headaches, and mastalgia.
- Treatment with flutamide has been associated with fatal hepatotoxicity.
- Treatment with ketoconazole has been associated with serious hepatotoxicity.
- Treatment with finasteride has been associated with minimal gastrointestinal side effects, in addition to having the potential of causing ambiguous genitalia in a male fetus if taken by a woman during pregnancy.

- Because of the severe hypoestrogenemia induced by gonadotropin-releasing hormone agonists, a concurrent add-back therapy with estrogen and progesterone (the latter when the uterus is present) is essential. This therapy will also correct the severe vasomotor symptoms and other side effects of the resulting hypoestrogenemia.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Contraindications to use of oral contraceptives may be a history of phlebitis, severe migraine, substantial weight gain, and the risk of increased insulin resistance.
- The occurrence of lactic acidosis is extremely rare with metformin and is more likely in those patients with renal impairment. Use of metformin should be discontinued before administration of contrast dye, particularly in subjects with decreased renal function.
- Treatment with antiandrogens, insulin-sensitizing agents, and 5 alpha-reductase-inhibiting agents is contraindicated during pregnancy.

QUALIFYING STATEMENTS

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These guidelines are not to be considered an extensive review of the literature on this topic or an exhaustive analysis of recent advances in this field. They are intended to be what the word guidelines implies: a brief summary of the accepted scientific information and views on this topic as well as suggestions for the diagnosis and treatment of these disorders. The presented material is in a form that can be easily used and applied to practical clinical situations encountered by endocrinologists.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

AACE medical guidelines for clinical practice for the diagnosis and treatment of hyperandrogenic disorders. *Endocr Pract* 2001 Mar; 7(2):120-134. [86 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001 Mar-Apr

GUIDELINE DEVELOPER(S)

American Association of Clinical Endocrinologists - Medical Specialty Society

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GUIDELINE COMMITTEE

Hyperandrogenic Disorders Task Force

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the [American Association of Clinical Endocrinologists \(AACE\) Web site](#).

Print copies: Available from the American Association of Clinical Endocrinologists (AACE), 1000 Riverside Avenue, Suite 205, Jacksonville, FL 32204.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on September 26, 2001. The information was verified by the guideline developer on November 11, 2002.

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