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Polycystic ovary syndrome: Pathogenesis and treatment over the short and long term

ABSTRACT

Although polycystic ovary syndrome (PCOS) is associated with hyperandrogenism and infertility early in life, it is a harbinger of a lifelong condition that can lead to serious sequelae such as endometrial or ovarian cancer, diabetes mellitus, and coronary artery disease. We review the pathophysiology, diagnosis, and treatment of this condition.

KEY POINTS

PCOS, characterized by amenorrhea, hirsutism, and infertility, is caused by a complex interaction of abnormalities in gonadotropins, androgens, and estrogens. Insulin resistance and hyperinsulinemia contribute significantly to its underlying pathophysiology.

Nonpharmacologic measures are universally recommended; these include diet, exercise, and weight reduction if the patient is obese or insulin-resistant.

Pharmacologic treatments include oral contraceptives, antiandrogen drugs (usually spironolactone), gonadotropin-releasing hormone agonists, glucocorticoids, and insulin sensitizers.

Lifelong monitoring for cancer, diabetes, and coronary artery disease is crucial.

POLYCYSTIC OVARY SYNDROME (PCOS) is not merely a reproductive disorder. Although the hyperandrogenism and infertility that PCOS causes are distressing to young women, its metabolic consequences eventually plague them the most in terms of morbidity and mortality.

Thus, it is crucial to diagnose PCOS early in its course not only to recognize but also to delay or arrest its metabolic sequelae. In addition, screening for the expected complications may allow for proper and timely management of these conditions.

PCOS IS COMMON

PCOS affects 5% to 10% of women of reproductive age,¹ making it the most common endocrine disorder of women in this age group. It is often seen in general internal medicine practice.

PRESENTATION

Characterized by oligomenorrhea, amenorrhea, infertility, and hirsutism occasionally but not invariably in association with enlarged cystic ovaries, PCOS was first described in 1935 by Stein and Leventhal.²

Amenorrhea. Up to 10% of patients presenting with primary amenorrhea and 75% of those with secondary amenorrhea fulfill the criteria for PCOS (**TABLE 1**). (*Primary amenorrhea* means never having had menses; *secondary amenorrhea* means absence of menses for more than 3 months after having had menses.)

*The author has indicated that he is on the speaker's bureaus of the Bristol-Myers, GlaxoSmithKline, Knoll, Eli Lilly, Pfizer, and Takeda corporations.

This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

TABLE 1

Criteria for diagnosis of polycystic ovary syndrome (PCOS)

Major criteria

- Chronic anovulation
- Clinical signs of androgen excess
 - Hirsutism
 - Acne
 - Alopecia
 - Menstrual disturbance
 - Infertility
 - Virilization
- Exclusion of alternative causes of androgen excess

Minor criteria

- Insulin resistance
- Onset at puberty
- Elevated LH:FSH ratio (> 2.5–3)
- Ultrasonographic evidence of polycystic ovaries

Rapid, severe virilization suggests a tumor

Menstrual irregularities are common in PCOS, but women with PCOS may have intermittently regular and fertile cycles in spite of elevated androgen levels.

Signs of androgen excess. Hyperandrogenism typically causes hirsutism, acne, and male pattern balding.

Hirsutism is the excessive growth of terminal, medullated, and pigmented hair on androgen-sensitive areas of skin such as the chin, upper lip, sideburns, and the sternal, periareolar, umbilical, and sacral areas, with accentuated involvement in the pubic region and upper thighs (male escutcheon). Alopecia is a much rarer manifestation of PCOS.

Acne can be seen in one of two to three normal women perimenstrually, but severe cystic and persistent acne is usually androgen-dependent.

Virilization is usually mild. More severe signs such as clitoromegaly, deepening of the voice, and increased muscle mass are rare; if they are present, underlying diseases of the adrenal and pituitary glands, including congenital adrenal hyperplasia, hyperprolactinemia, or androgen-secreting tumors, need to be excluded as causes. Rapid, severe virilization with clitoromegaly and muscle changes suggestive of a male habitus usually indicate a virilizing tumor.

Onset is usually at puberty, and the hyperandrogenic effects usually progress slowly

over time. Patients with PCOS typically present to their primary care physicians with initial complaints of hirsutism, acne, irregular menses, and perhaps infertility. If pregnancy does occur, there is an increased risk of gestational diabetes and pregnancy-induced hypertension.³

Obesity, especially central visceral obesity, is present in 35% to 80% of patients with PCOS, reflecting that most, but not all, patients with PCOS are insulin-resistant.⁴ The insulin resistance and hyperinsulinemia can also be clinically manifest as varying degrees of hyperpigmentation in skin fold creases or as frank acanthosis nigricans.

Metabolic problems usually develop with age. Specifically, PCOS predisposes women to a higher risk of developing the metabolic syndrome, consisting of type 2 diabetes mellitus, dyslipidemia, hypertension, and cardiovascular disease, and a higher risk of endometrial and ovarian cancer.³

■ PATHOPHYSIOLOGY

The exact pathophysiology of PCOS and its initiating event have yet to be elucidated. However, various biochemical abnormalities have been described, and associations and linkages of one to another have been established. Many of these abnormalities reinforce each other in vicious circles (FIGURE 1).

Hypothalamic-pituitary abnormalities

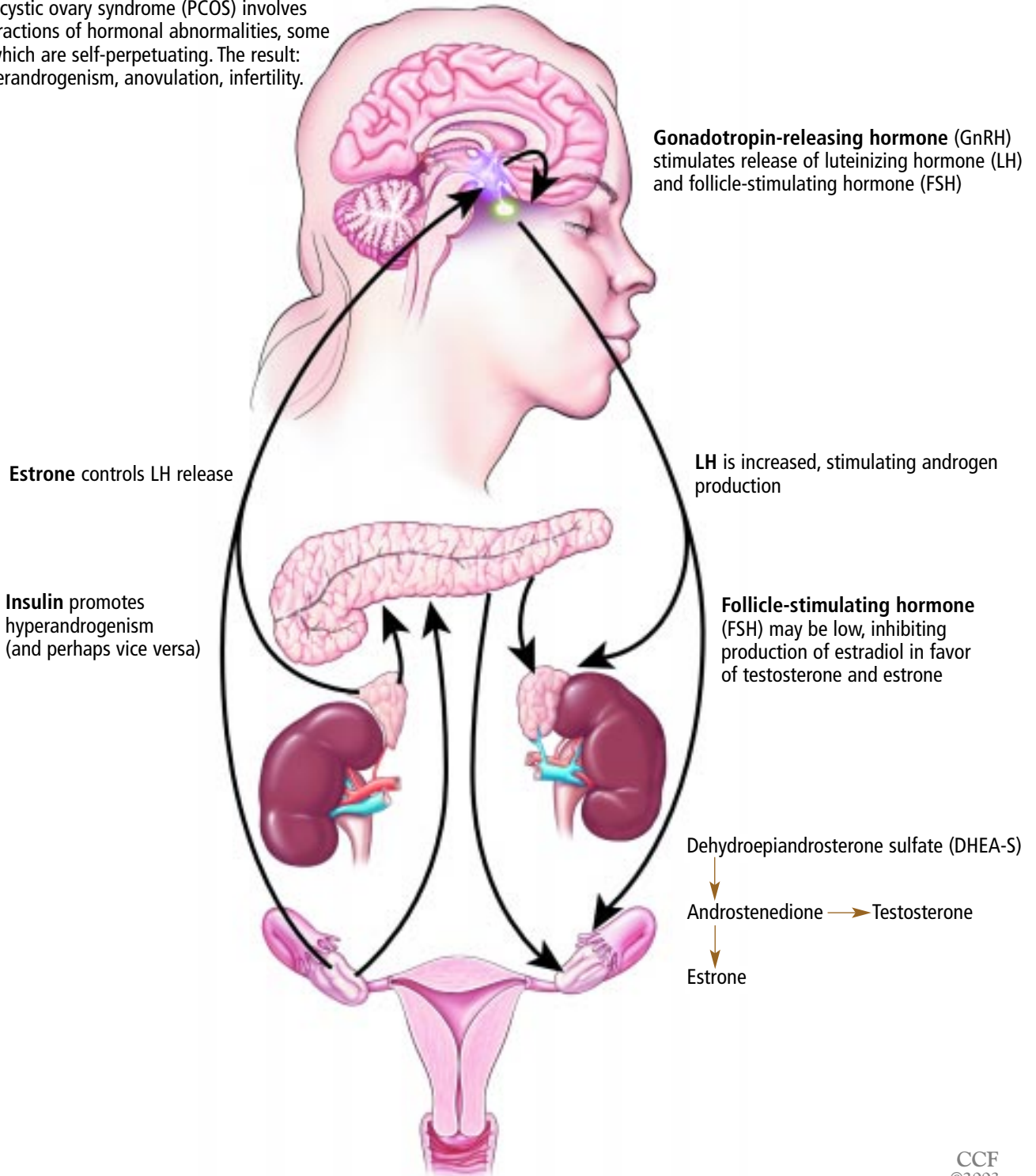
Elevated LH, low-normal FSH. In PCOS, the normal pulsatile secretion of luteinizing hormone (LH) is increased by an increased frequency and amplitude of pulses, while that of follicle-stimulating hormone (FSH) is unchanged or muted. Thus, LH values may be elevated, and the LH:FSH ratio can be increased to more than 2.5, even in ovulatory cycles. On the other hand, these values may be normal in as many as 10% to 20% of women with PCOS.⁵

Elevated GnRH. The inappropriate secretion of gonadotropins is thought to be due to an abnormality of the gonadotropin-releasing hormone (GnRH) pulse generator in the hypothalamus. It remains unclear whether this is a primary abnormality or a secondary one.



■ What causes polycystic ovary syndrome?

Although the inciting event is not known, polycystic ovary syndrome (PCOS) involves interactions of hormonal abnormalities, some of which are self-perpetuating. The result: hyperandrogenism, anovulation, infertility.



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FIGURE 1

Evidence that it is a primary defect comes from studies in young girls with a family history of PCOS who were entering puberty.^{6,7} Instead of the typical LH pulsatility at night seen in early puberty, LH pulses in these young girls started in the late afternoon. This indicates that the GnRH pulse generator is disrupted very early in reproductive life.

Evidence that the abnormality in the GnRH pulse generator is secondary: women develop a PCOS-like condition if they have Cushing syndrome, are exposed to anabolic steroids, or have androgen-producing tumors. Correcting the primary abnormalities usually reverses the condition. However, there is no evidence linking hyperinsulinemia or insulin resistance to the development of a GnRH pulse generator abnormality.

Elevated prolactin. Prolactin levels are elevated in about 25% of patients with PCOS. Extreme elevations of prolactin may stimulate adrenal production of dehydroepiandrosterone sulfate (DHEA-S).

Hyperandrogenism

All patients with PCOS have an increased sensitivity to androgens; up to 70% have elevated androgen levels, and the other 30% are in the high-normal range.

There are three major circulating androgens:

- Androstenedione (of which > 90% is produced in the ovaries)
- DHEA-S (mainly produced in the adrenal glands)
- Testosterone (produced from the ovaries and adrenal glands in equal amounts).

Ovarian abnormalities

Androstenedione is produced by the ovarian stromal and thecal cells in response to LH. It is normally converted to estradiol by an FSH-dependent aromatase. Excess androstenedione in the circulation is converted to estrone, which exerts a tonic effect on LH production while contributing to a relative suppression of FSH production.

In the face of a high LH:FSH ratio, as in PCOS, more androstenedione is synthesized but is not aromatized, thus perpetuating a vicious cycle driving LH production and some prolactin production.

Testosterone. The ovary converts some androstenedione to testosterone, and in PCOS this is amplified. Circulating testosterone comes from the ovaries and from peripheral conversion.

Abnormalities of estrogen

Estrogen secretion is usually abnormal in PCOS.

Estradiol levels may be low to normal, and in the anovulatory cycle there is tonic production without the increase before ovulation or in the midluteal phase as in normal women.^{8,9}

Estrone levels increase due to extraglandular conversion of androstenedione in adipose tissue, which further stimulates LH and inhibits FSH secretion, causing stimulation and hyperplasia of the ovarian stroma and theca cells, leading to increased androgens. This provides more substrate for extraglandular aromatization of androgens to estrogens and perpetuates the cycle.

Adrenal abnormalities

Excess adrenal androgen generated during stress or adolescence or due to congenital adrenal hyperplasia because of enzyme defects might initiate the cycle of abnormal LH/FSH stimulation and lead to PCOS.

DHEA-S. Pituitary gonadotropin does not directly stimulate adrenal androgens, but prolactin can stimulate DHEA-S. In the adrenal glands, DHEA-S is co-secreted with cortisol. Thus, most excess cortisol secretion, as in stress or in adolescence, is accompanied by an elevation of DHEA-S secretion, even in the face of normal corticotropin secretion. At the same time, elevated levels of prolactin, seen in as many as 25% of patients with PCOS, also enhance DHEA-S secretion. While DHEA-S has little androgenic activity, small amounts can be converted to androstenedione and subsequently to testosterone.

Peripheral abnormalities

Decreased SHBG. Elevated levels of androgens in the circulation, especially testosterone, inhibit production of hepatic sex hormone-binding globulin (SHBG). With less SHBG in circulation, more androgens are left

In PCOS, LH may be high, FSH low to normal



free or unbound and therefore produce a greater clinical response in terms of hirsutism, acne, and other manifestations of androgen excess. Thus, hyperandrogenism begets more hyperandrogenism and amplifies the action.

Insulin resistance and hyperinsulinemia

Insulin resistance is present in a large percentage of women with PCOS, especially if obese, irrespective of ethnicity.

Because hyperandrogenism and hyperinsulinemia coexist in PCOS, the important question is whether one causes the other. There is no question that exogenous or tumorous hyperandrogenism can result in glucose intolerance and elevated insulin levels.^{10,11} Lowering such hyperandrogenism improves insulin resistance and acanthosis. Numerous mechanisms might explain such a link.¹²⁻¹⁴

However, the data for hyperandrogenism causing hyperinsulinemia are not conclusive. Numerous reports show that lowering androgen levels¹⁵ or attenuating their effects¹⁶ does not reduce hyperinsulinemia in women with PCOS. Conversely, induced hyperandrogenism in women without PCOS¹⁷ or in animal models¹⁸ does not alter insulin sensitivity. Furthermore, the insulin resistance does not seem to be due to the hyperandrogenism, since it persists after oophorectomy¹⁹ or after ovarian androgen synthesis is suppressed by GnRH agonists.¹⁶

Abundant evidence indicates that hyperinsulinemia begets hyperandrogenism.^{17,20,21} Giving insulin to women with PCOS increases their circulating androgen levels,¹⁷ and lowering insulin by administration of diazoxide lowers their androgen levels.^{16,19} Furthermore, insulin sensitizers such as metformin²² and thiazolidinediones²³ have been shown to reduce androgen levels and facilitate follicular maturation, normal menses, and pregnancy.

In vitro, insulin has been shown to stimulate androgen production in the thecal cells of women with PCOS,²⁴ but not in normal women. Furthermore, insulin amplifies the LH response of granulosa cells, thereby causing an abnormal differentiation of these cells, premature arrest of follicular growth, and, so, anovulation.

While PCOS is associated with insulin resistance and hyperinsulinemia, the ovary

itself is not insulin-resistant and, in fact, possibly responds excessively to the hyperinsulinemia. Cell surface insulin receptors are at normal levels, but there is a postreceptor defect in signal transduction, causing a decrease in glucose transport.

Recently it has been suggested that the postreceptor binding defect is an increase in insulin receptor-mediated serine phosphorylation with a concomitant decrease in protein kinase activity and necessary tyrosine kinase activity, thereby interfering with transduction of the insulin signal and causing it to be defective.¹ This abnormality persists in cells cultured from PCOS ovaries and is not seen in cell cultures from normal ovaries, suggesting a genetic basis for their abnormality.

Although PCOS can be familial, genetic studies have failed to reveal any specific gene markers or chromosomal abnormalities associated with the disorder.

Insulin may increase androgen synthesis by various mechanisms. It may directly increase ovarian androgen synthesis by interacting with its own receptor or with the receptor for insulin-like growth factor-1, thereby increasing P450c17-alpha enzyme activity. It may not only cause or worsen the altered LH secretion seen in PCOS, but may change the ovarian response to LH, as described above. It also suppresses hepatic production of SHBG, which increases free testosterone levels. Thus, insulin alters normal folliculogenesis by increasing intraovarian androgens, by altering gonadotropin release, or by direct effects on the ovary.

■ LONG-TERM CONSEQUENCES

Endometrial and ovarian cancer

In PCOS, estrogen's effect on the endometrium is unopposed due to lack of cyclical progesterone, thus predisposing to endometrial cancer.

In the ovary, the inability to produce estradiol because of the decreased activity of FSH-related aromatase attenuates the development of ovulatory follicles, thereby causing the development of a large number of follicles in various stages of arrested maturation and accelerated senescence, giving rise to the typical picture of polycystic ovaries, while also

Ovaries need not be polycystic for a diagnosis of PCOS

producing higher levels of inhibin, accentuating the FSH suppression.

Furthermore, the lack of follicular maturation causes anovulation, while the low or normal estradiol levels together with the elevated estrone predispose to the unopposed growth of the endometrium. The lack of cyclical progesterone because of anovulation allows for unopposed endometrial growth, which is only partially shed during episodes of dysfunctional uterine bleeding, predisposing to the later development of endometrial cancer.

At the same time, the tonic and abnormal stimulation of the ovary is thought to be related to a higher incidence of ovarian cancer in later years in these patients.

Diabetes

The association between hyperinsulinemia and hyperandrogenism was first described in 1980 by Burghen et al²⁵ and led to the realization that in addition to hirsutism and infertility, PCOS has associated metabolic risks. From 20% to 40% of obese women have impaired glucose tolerance or type 2 diabetes mellitus, usually developing by the third to fourth decade of life. This association is seen in different ethnic groups, in both obese and lean women with PCOS, and to a greater degree than in age-matched and weight-matched normal women.

Coronary artery disease

Insulin resistance is the etiopathologic cause of the newly described metabolic syndrome, characterized by increased waist circumference (> 35 inches in women), low high-density lipoprotein cholesterol (HDL), high triglycerides, high blood pressure (> 130/80 mm Hg), and increased fasting glucose (> 100 mg/dL). It is beyond the scope of this article to elucidate the exact way insulin resistance causes all of the other factors, but it is crucial to point out that the incidence of coronary artery disease is twofold to fivefold higher in individuals with the syndrome, which is very common in the later years of most patients with PCOS.

DIAGNOSIS

The diagnosis of PCOS is primarily clinical. A consensus conference convened by the

National Institutes of Health (NIH) in 1990 proposed that the criteria for diagnosis should be features of hyperandrogenism with chronic anovulation after identifiable causes are excluded (TABLE 1). Menarche may be normal or delayed, and either amenorrhea, oligomenorrhea, or dysfunctional uterine bleeding may occur.²⁶ Not all the criteria need to be present for the diagnosis, however.

Polycystic ovaries are not a requirement for diagnosis, nor are they sufficient for diagnosis, since they may occur in up to 20% of normal women, as well as in women with isolated oligomenorrhea or hyperandrogenism.^{3,27}

Laboratory evaluation

If the NIH clinical criteria are present, the patient should undergo laboratory evaluation to exclude hyperprolactinemia, late-onset congenital adrenal hyperplasia, and androgen-secreting tumors of the ovary or adrenal gland. Normal serum levels of the following hormones can exclude these disorders:

- Prolactin
- Testosterone
- DHEA-S
- Corticotropin-stimulated 17-alpha-hydroxyprogesterone.

Although not essential to the diagnosis, insulin resistance is common and may affect treatment decisions. Therefore, fasting blood glucose and insulin levels can be measured to evaluate for hyperinsulinemia.

TREATMENT

In the 1930s, Stein and Cohen²⁸ incidentally found that ovarian wedge resection led to resumption of normal menses and occasionally conception. Unfortunately, the syndrome reappeared in most patients.

The traditional treatment of PCOS is aimed at the clinical features and depends on the manifestations that are most bothersome to the patient. Response to therapy is slow, with biochemical reversal preceding clinical change by as much as 6 to 9 months. Treatment of acne, hirsutism, and menstrual irregularities when fertility is not an issue requires a concerted effort on many fronts.

Oral
contraceptives
are of
particular
benefit in PCOS



Nonpharmacologic measures

Nonpharmacologic measures are universally recommended; these include diet, exercise, and weight reduction if obese or to reestablish some degree of insulin sensitivity.

Although long-term success may be variable and adherence can be a challenge, studies have shown a significant reduction in androgens and reestablishment of ovulatory cycles with a loss of as little as 10 to 15 pounds over 6 months.²⁹ Hirsutism can improve in the first 6 to 9 months, concomitant with weight loss, and regular menstrual cycles can occur at the same time as lowering of androgen levels.

The metabolic consequences of PCOS also improve with nonpharmacologic measures, with reductions in hyperinsulinemia, P450c17 activity in the ovary, plasminogen activator inhibitor-1 activity, and triglycerides, and a concomitant increase in HDL cholesterol.

Oral contraceptives

Oral contraceptives are useful in patients with PCOS who do not desire pregnancy. Besides establishing regular menstrual cycles, they reduce gonadotropin stimulation of the ovary and thereby reduce androgen production.³⁰ They also cause an increase in SHBG while inhibiting 5-alpha reductase and androgen-receptor binding. Hirsutism and acne respond well to oral contraceptive use.

It is important to choose the appropriate oral contraceptive. Newer progestins such as desogestrel, as well as norgestimate and ethynodiol diacetate, have minimal androgenic potential and are considered to be superior to preparations containing norgestrel or norethindrone, which have more androgenic properties.

Antiandrogens

Many patients show a further benefit from the addition of an antiandrogen to an oral contraceptive.

Spironolactone is the antiandrogen most often used in the United States.

Spironolactone acts mainly by blocking the androgen receptor from "seeing" dihydrotestosterone. It may also suppress 17-hydroxylase and 17,20-lyase activity, thereby blocking androgen biosynthesis. However,

because it has a minimal antigonadotropic effect, it has a minimal effect on free testosterone and androstenedione when used without a concomitant oral contraceptive.

A 40% to 80% reduction in sexual hair growth can be seen with spironolactone.³¹ When used for alopecia, it reduces hair loss but has a minimal effect on hair regrowth. Spironolactone requires 8 to 14 months before its clinical effects can be seen.

We strongly recommend that spironolactone be used with adequate contraception to offset the theoretical risk of teratogenicity to the male fetus and to minimize its effect on the endometrium; when used alone, it can cause polymenorrhea.

Other side effects of spironolactone include headache, mood swings, fatigue, reduced libido, mastodynia, hyperkalemia, gastrointestinal discomfort, and irregular menstrual bleeding.

The dosage is 50 to 100 mg per day in divided doses, though up to 200 mg can be used.

Other antiandrogens not available in the United States (cyproterone) or not approved by the US Food and Drug Administration for uses related to PCOS (flutamide) seem to have clinical effects very similar to those of spironolactone.³²

Cimetidine and ketoconazole have a very limited role to play in the treatment of PCOS, mainly because their side effects far outweigh their clinical benefits.

Finasteride, a 5-alpha reductase inhibitor, has been used because it blocks the conversion of testosterone to dihydrotestosterone and decreases androgen-receptor binding.³³ It is as effective as spironolactone. Adequate contraception is essential because of risk to the male fetus.³⁴

Gonadotropin-releasing hormone agonists

Gonadotropin-releasing hormone agonists have been used, especially in severe ovarian hyperandrogenism.³⁵ Depot preparations, given monthly, result in a medical menopause that is reversible. Oral contraceptives are required to overcome menopausal symptoms and to prevent premature bone loss—4% to 8% after 6 months of therapy without concomitant oral contraceptives.

Spironolactone must be used only with adequate contraception

If hyperprolactinemia is present, bromocriptine may help to establish cyclicality and ovulation in some women with PCOS.³⁶

When fertility is desired

When fertility is desired, oral contraceptives and antiandrogens cannot be used. Sometimes, weight loss causes menses to become regular, although ovulation does not always occur. Patients may require fertility drugs such as clomiphene citrate or exogenous gonadotropins. Nowadays, insulin sensitizers, especially metformin, are playing an increasing role in establishing fertility.

Steroids

Glucocorticoids have long been known to be helpful if oral contraceptives and spironolactone do not suppress DHEA-S or testosterone adequately. Dexamethasone 0.125 to 0.25 mg or prednisone 2.5 to 5.0 mg can be used; the dose should be given in the evening to blunt corticotropin stimulation of the adrenal glands the following morning.³⁷ Ovulatory cycles can be established, but the response of hirsutism is variable and limited.

Higher doses may be associated with adrenal suppression and the development of cushingoid features in some patients; therefore, clinical monitoring is crucial.

Once pregnancy is established, it is a conservative recommendation to continue low-dose steroids through the first trimester to offset the luteotropic effect of androgens and prevent early miscarriage.

Insulin sensitizers

Given the strong association and possible pathophysiologic relationship between insulin resistance and PCOS, insulin sensitizers have begun to play a more significant role in its treatment.

Metformin, a biguanide, inhibits hepatic glucose output and, to a lesser extent, enhances muscle glucose uptake, lowering insulin levels.

Metformin has been extensively studied. In some clinical studies, metformin therapy was associated with a decrease in hyperinsulinemia and a consequent improvement in reproductive efficiency. Treated patients either ovulated spontaneously or showed an

ovulatory response to clomiphene while on metformin, which was not seen when clomiphene was given alone in the same patients.³⁸

The effect of metformin seems not to be mediated by the drug's effect on weight loss, since even patients who did not lose weight while on metformin still showed an amelioration of the PCOS.

The improvement in ovulatory efficiency is associated with a change in testosterone levels and an increase in SHBG.

Side effects include gastrointestinal distress and variable, usually transient, flatulence and diarrhea. Metformin cannot be used in patients with renal impairment (serum creatinine level > 1.4 mg/dL), congestive heart failure, or liver dysfunction or for the 48 hours surrounding radiographic dye studies.

The doses of metformin most often used are between 1,500 and 2,000 mg per day.

Troglitazone, a thiazolidinedione, was used to treat PCOS before it was removed from the market. The thiazolidinediones improve peripheral glucose uptake in muscles and adipose tissue and also inhibit hepatic glucose output, thereby decreasing circulating insulin levels. They usually cause weight gain, underscoring that insulin sensitivity and lowering of insulin levels is the reason for improvement in ovulatory function.

While troglitazone was shown to decrease ovarian androgen production and improve ovulatory cycling and hirsutism, neither of the currently available thiazolidinediones (pioglitazone and rosiglitazone) has been studied in this regard.

The theoretical risk of hepatotoxicity and, more importantly, teratogenic risk make this class of drugs less likely to be used in the near future.

Nonsystemic hair removal

Hirsutism may be managed by mechanical means such as bleaching, plucking, waxing, shaving, depilatory creams, electrolysis, and laser therapy. The latter two options are more expensive. Electrolysis generally requires long-term treatments. Laser therapy has been reported to be most successful in women with light skin and dark hair.

Continue low-dose steroids through the first trimester of pregnancy in women with PCOS



Eflornithine (Vaniqa), a new topical agent for reducing hirsutism, interferes with an enzyme in the hair follicle and slows hair growth. Mechanical hair removal is still required, and improvement is gradual over 6 to 8 weeks. It is applied to areas of facial hair twice a day. Temporary redness, stinging, burning, tingling, rash, or folliculitis may occur. By 8 weeks after stopping treatment, the hair will reappear to the same extent as before starting eflornithine.

Monitoring for and preventing the consequences of PCOS

It is crucial to remember that the metabolic consequences of PCOS far outlast the child-bearing years. The incidence of the later development of hypertension, dyslipidemia, diabetes, and coronary artery disease is significantly higher with PCOS.

Thus, to prevent long-term morbidity and mortality, it is mandatory to give appropriate and intensive counseling about preventive measures such as diet and weight loss and to treat risk factors aggressively. In the same vein, surveillance monitoring for ovarian and especially endometrial malignancies is crucial.

WHO SHOULD MANAGE PCOS?

PCOS has evolved out of the purview of the reproductive endocrinologist. The syndrome truly involves a number of subspecialists, including dermatologists, endocrinologists, gynecologists, and, in the long run, cardiologists, nephrologists, and oncologists.

The team is probably best quarterbacked by an internist or endocrinologist, and a clear understanding of the pathophysiology of PCOS is crucial for its treatment through the different phases of a woman's life.

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Insulin sensitizers are playing a bigger role in PCOS treatment



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Brief descriptive lead-in headings for word ads (eg, "Hospitalist Opportunities, Portland, Oregon," "Northeast Pennsylvania Group Practice") will be set in bold type at the beginning of the ad, **for up to three lines of type**, when indicated by the advertiser. Bold type is not otherwise available for word ads.

Frequency Discount Policy

To earn the reduced rate for 2 or more insertions, you must indicate upon first placing your ad that you are running it in two or more consecutive issues.

Reply Box Service

Confidential box numbers are available for \$25 per insertion. Responses will be forwarded to the advertiser via first-class mail.

Deadline, Changes/Cancellations

All ad orders must be received 6 weeks prior to the publication issue date (eg, by December 15 to appear in the February issue). CCJM is published monthly. Any cancellations or changes must be received in writing by this same deadline.

Proofs

For word ads and for display ads that we typeset, advertisers will be sent a proof of their ad (via fax or e-mail) prior to publication, **solely to verify accurate reproduction of the originally submitted copy**. Corrections must be received within 2 business days of when we send the proof. No changes to the submitted copy can be guaranteed if made beyond the deadline (6 weeks prior to issue publication date).

How to Place an Ad

All ads must be submitted in digital form or in writing. Send ad copy or digital file via e-mail to ccjm@ccf.org, or fax ad copy to CCJM Classifieds at 216-444-9385. Direct production inquiries to Bruce Marich at marichb@ccf.org or 216-444-1156. All orders will be invoiced. Indicate person and postal address to which invoice should be sent. Payment is accepted by check or credit card (Visa or MasterCard).

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