PART 4 OF A 4-PART E-SERIES

Polycystic ovary syndrome: Cosmetic and dietary approaches

What we know about treatment of hirsutism and acne, the effects of weight loss, and emerging diagnostic tests

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Although polycystic ovary syndrome (PCOS) is the most common endocrine abnormality in women of reproductive age, affecting at least 1 in 15 women in this population, its precise cause is unknown. As a result, management of PCOS requires a focus on its individual effects, among them anovulation, infertility, hyperandrogenism, and insulin resistance.

So far in this four-part series, we have covered diagnosis and treatment, the role of obesity and insulin resistance, and long-term metabolic risks. In this concluding article, we focus on cosmetic and dietary issues, and describe emerging diagnostic approaches to this common disorder.

Q My patient has excessive hair growth and acne and only cares about cosmetic results. Other than the traditional therapy of oral contraceptives (OCs), what medical treatment options does she have?

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Management of hirsutism and acne should focus on combination therapy that includes androgen suppression and peripheral androgen blockade, with or without mechanical or cosmetic reduction or destruction of unwanted hair. The choice of treatment depends on the side-effect profile. To maximize benefits, treatments should be continued for at least 2 years. All of the therapies described in this article have teratogenic potential (inhibiting normal development of male external genitalia) and should be prescribed only with adequate contraception that is used consistently.

Medical treatment of hirsutism and acne

Oral contraceptives are the most popular treatment for hirsutism. They suppress pituitary production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which in turn suppress ovarian androgen production. OCs also may reduce adrenal androgen production, although the mechanism of action is unclear.

The estrogen component in OCs increases hepatic production of sex hormone-binding globulin (SHBG), thereby decreasing free testosterone levels. The progestin component antagonizes 5α-reductase

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Drug	Brand name	Cost	Side effects
Spironolactone	Aldactone, Novo-Spiroton, Aldactazide, Spiractin, Spirotone, Verospiron, Berlactone	$30 for thirty 50-mg tabs	Dyspepsia, nausea, polyuria, nocturia, fatigue, headache, breast tenderness, reduced libido, photosensitivity, hyperkalemia (rare)
Flutamide	Eulexin	$170 for one hundred 250-mg tabs	Greenish urine, excessive dryness of skin and scalp, liver enzyme abnormalities, hepatic toxicity
Bicalutamide	Casodex, Cosudex, Calutide, Kalumid	$30–$490 for thirty 50-mg tabs	Breast tenderness, gynecomastia, hot flushes, gastrointestinal disorders, diarrhea, nausea, hepatic changes, asthenia, pruritus
Cyproterone acetate	Androcur, Cyprostat, Cyproteron, Procur, Cyprone, Cyprohexal, Ciproterona, Cyproteronum, Neoproxil, Siterone	$35–$50 for twenty 50-mg tabs (generic) $90 for sixty 50-mg tabs (Androcur)	Liver toxicity, adrenal insufficiency, loss of libido, and depressive mood changes
Finasteride	Proscar, Propecia	$8.75–$17.50 for thirty to sixty 5-mg tabs	Teratogenicity is a major concern

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Early studies suggest that a dose of bicalutamide of 25 mg daily produces significant improvement in Ferriman-Gallwey scores

and the androgen receptor; it also may increase hepatic metabolism of testosterone and can increase SHBG when the OC has low androgenic activity.

Spironolactone is an aldosterone antagonist and mild diuretic that competes primarily with androgens for the androgen receptor. It also:

- inhibits the 5α-reductase enzyme, preventing the conversion of testosterone to the more potent dihydrotestosterone (DHT)
- increases hepatic production of SHBG, thereby decreasing free testosterone levels
- suppresses enzymes in the biosynthesis of androgens.

A dose of 100 mg twice daily is effective, although higher doses of 200 mg to 300 mg may be required. Start with a dose of 25 mg daily, with a progressive increase over 3 weeks to minimize side effects (**TABLE**).

Flutamide (Eulexin) is approved by the US Food and Drug Administration as an adjuvant treatment for prostate cancer. It is not a steroid but a substituted anilide that competes with testosterone and its powerful metabolite, DHT, for binding to androgen receptors. Flutamide may also be used to treat excess androgen levels and hirsutism in women. It is given at a dose of 500 mg daily. Side effects include greenish urine, excessive dryness of skin and scalp, liver enzyme abnormalities, and hepatic toxicity.

Flutamide is now being replaced by a newer member of this class of drugs, **bicalutamide** (launched in 1995 and marketed as Casodex, Cosudex, Calutide, Kalumid), due to a better side-effect profile. Bicalutamide acts as a pure antiandrogen by binding to the androgen receptor and preventing its activation and subsequent upregulation of androgen-responsive genes by androgenic hormones. In addition, bicalutamide accelerates the degradation of the androgen receptor. Preliminary studies suggest that a dose of 25 mg daily produces significant improvement in Ferriman-Gallwey scores. Side effects include breast tenderness, gynecomastia, hot flushes, gastrointestinal disorders, diarrhea, nausea, hepatic changes (elevated levels of transaminases; jaundice), asthenia, and pruritus.

Cyproterone acetate is a synthetic derivative of 17-hydroxyprogesterone. It inhibits the steroidogenic enzyme 21-hydroxylase and, to a lesser extent, 3-beta-hydroxysteroid dehydrogenase, both of which are needed to synthesize cortisol and aldosterone.

Gonadotropin production is reduced by the progestational and glucocorticoid effects

of cyproterone acetate and may result in lower testosterone levels. However, the blockade of adrenal 21-hydroxylase may lead to the accumulation of androgen precursors, which may be converted to testosterone, reducing the efficacy of antiandrogen treatment. For this reason, cyproterone acetate is sometimes combined with other agents. Studies of hirsutism have demonstrated increased efficacy with combination therapy, compared with cyproterone acetate alone. This drug is approved for use only in the United Kingdom and Canada.

A dose of 50 mg to 100 mg is recommended. The most serious potential side effect is liver toxicity. Patients should be monitored for changes in liver enzymes, especially if they are taking a high dose (200–300 mg/day). Other side effects include adrenal insufficiency, loss of libido, and depressive mood changes.

Finasteride (approved in 1992 and marketed as Proscar, Propecia) is a synthetic antiandrogen that inhibits 5α-reductase, the enzyme that converts testosterone to DHT. It is used as a treatment for benign prostatic hyperplasia in low doses, and for prostate cancer in higher doses. A dose of 2.5 mg to 5 mg daily is typical for women with hirsutism.

In randomized clinical trials, finasteride has produced significant improvements in hirsutism, compared with placebo, but no significant differences compared with other therapies. Although the side-effect profile is less severe than that of other therapies, teratogenicity is a major concern.

Q We hear a lot about weight loss improving the clinical effects of PCOS. Are some dietary approaches more successful than others in PCOS?

Numerous dietary interventions have been explored in women with PCOS.[1] A few studies have involved manipulation of the dietary macronutrient profile, but only two have used a controlled study design to compare different macronutrient compositions. Two different groups tested a high-protein (30%) diet, compared with lower protein (15%), while keeping fat intake (30%) the same.[2,3]

In a study by Moran and colleagues, women were prescribed a reduced-calorie diet for 12 weeks, followed by a maintenance diet for 4 weeks.[2] There were no differences between the high-protein and low-protein groups in terms of weight or fat loss (as assessed by dual-energy x-ray absorptiometry). However, the 38% dropout rate was higher than anticipated, and the authors acknowledge that the inability to detect a difference between groups could be due to insufficient power.[2]

In the study by Stamets and colleagues, the same macronutrient profile was used, but for only 4 weeks—too short a time to detect much difference in weight loss.[3] Not surprisingly, no difference in weight loss was found between groups.

In both studies, dietary compliance and the rate of study retention were confounding and limiting factors.[2,3] To date, there is insufficient evidence that a particular dietary approach, such as modified macronutrient composition, will enhance weight loss in women with PCOS. However, general dietary and lifestyle modifications still remain the first line of therapy to address the metabolic consequences of PCOS for overweight and obese women.[1] In appropriate clinical situations, consideration should also be given to alternative weight-loss approaches, such as weight-loss medication or bariatric surgery.

Q Is the circulating LH/FSH ratio important in the diagnosis of PCOS? What is current opinion on this?

Although the fundamental pathophysiologic mechanism is unclear, both lean and obese women with PCOS have greater LH pulse frequency and amplitude, leading to increased 24-hour mean concentrations of LH. Because androgen production by theca cells is LH-dependent, it would seem to follow that the elevated LH levels seen in women with PCOS are responsible for excess androgen production. The most likely cause of anovulation is an FSH level too low to fully mature the follicles. FSH levels may be suppressed by negative feedback inhibition from midfollicular estradiol levels.

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General dietary and lifestyle modifications remain the first line of therapy to address the metabolic effects of PCOS for overweight and obese women

While the defect in PCOS is unknown, it is clear that there are altered gonadotropin dynamics. Nonetheless, current consensus is that elevated LH is not essential for the definition of PCOS, despite this frequent finding and the understanding that high LH levels have adverse effects on oocyte quality, maturity, pregnancy outcomes, and miscarriages.[4,5]

Q Are there any new tests on the horizon that will make the diagnosis of PCOS easier?

In recent years there has been increasing interest in anti-Müllerian hormone (AMH) (also known as Müllerian-inhibiting substance), which is exclusively of ovarian origin in women, as a marker of ovarian reserve and female reproductive function. Several studies on the role of AMH in ovarian physiology indicate that the hormone has two main functions with respect to folliculogenesis, at least according to mice models:

- It plays a negative role in follicular recruitment.
- It reduces preantral and antral follicle responsiveness to FSH.[6–8]

We know that serum AMH levels decline with age, as there is a decline in female reproductive function due to the reduction in the ovarian follicle pool and the quality of the oocytes. Undetectable AMH levels after premature ovarian failure have been reported, and oophorectomy in regularly cycling women is associated with the disappearance of AMH within 3 to 5 days. In contrast, AMH serum levels are normal in women affected by functional hypothalamic (hypogonadotrophic) amenorrhea.

In the past, FSH, inhibin B, and the antral follicle count have been the most reliable markers for investigating ovarian reserve during assisted reproductive treatment and predicting ovarian response to ovulation induction in intrauterine insemination and in vitro fertilization cycles, and are also useful in monitoring other reproductive disorders. However, AMH seems to better reflect the continuous decline of the oocyte/follicle pool with age and may be the best marker of ovarian aging and the menopausal transition. Moreover, serum levels can be drawn at any time of the menstrual cycle, unlike the measurement of FSH, which must be performed on day 3 of the cycle.[8,9]

Increased AMH production also has been reported in women with PCOS, compared with controls.[10] The increased production may be the result of aberrant activity of the granulosa cells in polycystic ovaries. AMH production may exert a paracrine negative control on follicle growth sufficient to prevent selection of a dominant follicle. Coupled with higher inhibin B levels, this may lead to a relative deficit of FSH in women with PCOS.

AMH measurement offers high specificity and sensitivity as a marker for PCOS. On this basis, it has been proposed that, in situations in which accurate ultrasonographic data are unavailable, AMH could be used instead of the follicle count as a diagnostic criterion for PCOS. Therapeutic interventions, including metformin administration to improve insulin resistance in women affected by PCOS, are associated with a reduction in both serum AMH levels and antral follicles. This suggests that the measurement of AMH could be used to evaluate treatment efficacy, may be a better predictor of ovarian hyperstimulation syndrome (OHSS) than body mass index, and could help direct the application of mild ovulation induction protocols to avoid moderate and severe OHSS.

There seems to be little doubt that research on AMH will continue in years to come. A clearer understanding of its effects on ovarian physiology may help clinicians find a role for AMH measurement in the field of reproductive medicine, thereby simplifying the diagnosis of PCOS and the evaluation of its treatment efficacy.

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Anti-Müllerian hormone assessment offers high specificity and sensitivity as a marker for PCOS

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