Polycystic ovary syndrome: A review for dermatologists

Part II. Treatment

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After completing this learning activity, participants should be able to describe the range of treatment options for the hyperandrogenic manifestations of polycystic ovary syndrome (PCOS), acne, hirsutism, and androgenetic alopecia, and demonstrate an understanding of the safety and efficacy of the pharmacologic treatments used for PCOS, including topical therapies, combined oral contraceptive pills, antiandrogen drugs, and insulin-sensitizing drugs.

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Dermatologists are in a key position to treat the manifestations of polycystic ovary syndrome (PCOS). The management of PCOS should be tailored to each woman's specific goals, reproductive interests, and particular constellation of symptoms. Therefore, a multidisciplinary approach is recommended. In part II of this continuing medical education article, we present the available safety and efficacy data regarding treatments for women with acne, hirsutism, and androgenetic alopecia. Therapies discussed include lifestyle modification, topical therapies, combined oral contraceptives, antiandrogen agents, and insulin-sensitizing drugs. Treatment recommendations are made based on the current available evidence. (J Am Acad Dermatol 2014;71:859.e1-15.)

Key words: acne; androgenetic alopecia; combined oral contraceptive pills; cyproterone acetate; drospirenone; hirsutism; insulin-sensitizing drugs; polycystic ovary syndrome; spironolactone.

Although patients with polycystic ovary syndrome (PCOS) often present to dermatologists with cutaneous concerns, it is essential to provide education regarding the metabolic and fertility-related implications of PCOS and to form a multidisciplinary team that includes a primary care physician and an endocrinologist. Understanding patients' reproductive goals and medical health allows providers to develop a comprehensive medical plan. The decision to begin pharmacologic treatment for dermatologic manifestations of PCOS must be tailored to each woman's specific concerns.

Pharmacologic treatment is not necessary for all patients with PCOS, and mild forms of hirsutism, acne, and androgenetic alopecia may be satisfactorily managed with standard nonhormonal agents (Table I) that—aside from laser hair removal, minoxidil, and eflornithine—will not be reviewed here.[1-4] In addition, a discussion of weight loss, diet, and exercise in obese patients may be helpful in managing cutaneous symptoms. This review focuses primarily on pharmacologic management of PCOS, because many patients find standard topical agents ineffective and are eager to target the hormonal cause underlying their dermatologic concerns.

Abbreviations used:

cOCP:	combined oral contraceptive pill
CPA:	cyproterone acetate
EE:	ethinyl estradiol
FDA:	US Food and Drug Administration
FG:	Ferriman–Gallwey
ISD:	insulin-sensitizing drug
PCOS:	polycystic ovary syndrome
SHBG:	sex hormone binding globulin
TZD:	thiazolidinedione
VTE:	venous thromboembolism

NONHORMONAL TREATMENTS

Key points

- **Changes in diet and exercise leading to weight loss improves fertility and metabolic findings, but studies conflict regarding efficacy on hirsutism and acne**
- **Topical nonhormonal therapies and laser hair removal may be effective for acne, hirsutism, and androgenetic alopecia in the PCOS population and are useful first-line agents**

Lifestyle changes

Lifestyle changes are often recommended as first-line treatment for PCOS to benefit overall health. Studies examining dietary interventions show conflicting effects on hirsutism, likely influenced by type of restrictive diet and study length, because studies often span weeks to months, which is not long enough to observe biologic changes on dermatologic effects. A study in 78 women found that of those who lost >5% body weight after 4 weeks of a calorie-restricted diet, 30% experienced improvement in hirsutism as measured using the Ferriman–Gallwey (FG) score (Fig 1); the other 70% of patients did not report improvement.[5] Other studies have also shown improvements in hirsutism with caloric restriction after 6 months.[6] However, a Cochrane review of 3 randomized, controlled trials concluded that there is no improvement in hirsutism after dietary changes.[7-9] In addition, there are insufficient data to suggest that lifestyle changes play a role in PCOS acne management.[10] However,

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Table I. Treatments for polycystic ovary syndrome

Lifestyle
Weight loss
Exercise
Glucose control
Hormonal
Combination estrogen and progesterone oral contraceptives
Antiandrogen: spironolactone, cyproterone acetate, drospirenone, and flutamide
Inhibition of peripheral androgen conversion: finasteride (5α-reductase inhibitors)
Insulin-sensitizing agents
Metformin
Thiazolidinediones
Nonhormonal
Acne: standard acne therapy, including topical retinoids, topical and oral antibiotics, benzoyl peroxide, topical dapsone, peels, and isotretinoin
Hirsutism: bleaching, shaving, waxing, electrolysis, laser hair removal, and eflornithine
Androgenetic alopecia: minoxidil

for other aspects of PCOS, such as weight and adiposity distribution, insulin resistance, and fertility, weight loss can be helpful.[10,11] Therefore, while additional research is needed, we continue to encourage lifestyle changes in PCOS patients.

Topical therapies

Topical therapies represent a safe starting point of treatment for androgenetic alopecia and hirsutism given their safety profiles. However, there have been no studies to date of minoxidil or eflornithine use specifically in PCOS.

Laser hair removal. Laser hair removal is a mainstay of treatment for hirsutism, but few studies exist in the PCOS population, and the limited data available conflicts regarding whether laser hair removal is as effective in patients with PCOS compared to those without.[12-14] However, all studies agree that laser hair removal is helpful and can reduce emotional burden and increase the quality of life of PCOS patients affected by hirsutism.[13] It should be noted that laser hair removal is ineffective on nonpigmented hairs, and potential side effects include pain, swelling, redness, and postinflammatory hyperpigmentation. Certain lasers are not advisable for use in patients with darker Fitzpatrick skin types. Laser hair removed is not often covered by insurance.[15]

Aside from a small study in 52 PCOS patients where metformin in addition to intense pulsed-light therapy significantly decreased hair count, laser hair removal has not been studied in conjunction with medical therapies.[16] Although it has been hypothesized that hormonal agents used concurrently with laser hair removal may maximize permanent laser hair removal by preventing chronic hair terminalization in patients with PCOS, this has not been studied.[14]

Minoxidil. Minoxidil is thought to promote hair growth via vasodilatation, enhanced cell proliferation and DNA synthesis, and increased angiogenesis.[17,18] Two concentrations of minoxidil (2% and 5%) are approved by the US Food and Drug Administration (FDA) for use in men, but only 2% is approved by the FDA for use in women. In 381 women treated twice daily for 48 weeks, 5% minoxidil was superior to placebo and increased hair growth by 24.5 hairs/cm^2 compared to 20.7 hairs/cm^2 with 2% minoxidil, although the difference was not statistically significant.[19] A single-blind study demonstrated equivalent efficacy between minoxidil 5% foam once daily and 2% solution twice daily in women.[20] Other studies exploring combined oral contraceptive pills (cOCPs)/minoxidil combination treatments have inconclusive results.[21]

Eflornithine hydrochloride cream. Eflornithine hydrochloride 13.9% cream slows hair growth by irreversible inhibition of ornithine decarboxylase, an enzyme that is necessary in hair follicle assembly.[22,23] Adverse effects include stinging, burning, and tingling.[24] Large randomized, controlled trials have shown statistically significant reductions in both hair length and mass with eflornithine treatment. A study of 594 women found a 23% reduction in hair length and a 26% reduction of hair mass.[24] One small randomized trial found a statistically significant difference in hair removal between eflornithine plus laser compared to laser alone.[25]

COMBINATION ORAL CONTRACEPTIVES WITH PROGESTINS DERIVED FROM 19-NORTESTOSTERONE

Key points

- **Combined oral contraceptive pills (ethinyl estradiol and a synthetic progestin) are the mainstay of therapy for patients with polycystic ovary syndrome**
- **Combined oral contraceptive pills differ in progestin androgenic activity and progestin dose. However, all combined oral contraceptive pills are antiandrogenic by virtue of ethinyl estradiol**

Mechanisms of action

cOCPS are the first-line pharmacologic therapy for PCOS patients who are not trying to conceive.[26,27] cOCPs are useful for contraception and effective

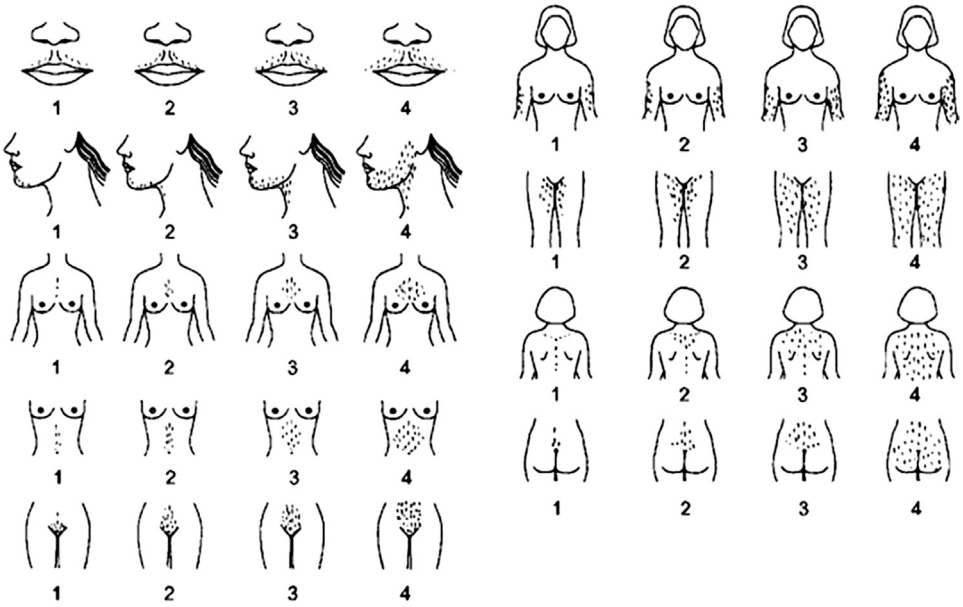

Fig 1. Modified Ferriman–Galwey scoring system. Nine body areas (ie, the upper lip, chin, chest, arm, upper abdomen, lower abdomen, upper aspect of the back, lower aspect of the back, and thighs) are scored as follows: 1 point (minimal terminal hairs), 2 points (hair growth is more than minimal but not yet that of a man), 3 points (hair growth is of a man who is not very hairy), and 4 points (equivalent to a hairy man). If no terminal hairs are present in the body area, the score is 0. Terminal hairs are typically longer than 0.5 cm and are usually pigmented. (Reprinted with permission from Yildiz et al,[191] figure 2, p 57, by permission of the Oxford University Press and from Dr R. Azziz.)

against menstrual irregularities and endometrial hyperplasia. cOCPs contain a low-dose ethinyl estradiol (EE) and synthetic progestin, the majority derived from 19-nortestosterone (Fig 2). Progestins derived from 19-nortestosterone differ from the progestins drospirenone and cyproterone acetate (CPA), which are unrelated to testosterone and antagonize the androgen receptor. These will be discussed separately. Generic equivalents are available for most cOCPs.

cOCPs function as antiandrogens in PCOS via 3 mechanisms. First, estrogen increases hepatic production of sex hormone binding globulin (SHBG), thereby decreasing circulating free testosterone levels. Second, progestin suppression of luteinizing hormone secretion decreases ovarian androgen production. Third, progestins compete to differing extents for 5α-reductase and the androgen receptor.[27-29] All cOCPs may be thought of as having a net suppressive effect on androgens, largely because of the action of estrogen on SHBG.[30] However, older 19-nortestosterone–derived progestins, including levonorgestrel, norgestrel, and norethindrone, may have more androgenic activity as measured by effects on SHBG and free testosterone. In contrast, newer 19-nortestosterone–derived progestins, specifically norgestimate, desogestrel, and gestodene, have less androgenic activity and do not significantly lower SHBG.[31,32] Androgenicity of progestins is dependent on both type and dosage; 2 cOCPs with the same progestin may have different androgenic activity based on estrogen doses and/or progestin. However, the clinical relevance of these differences on cutaneous features of PCOS is unclear.[33]

Many factors enter into the selection of a contraceptive method, including personal and family history, concurrent medications, and previous adverse effects of cOCPs such as breakthrough bleeding, headaches, nausea, breast tenderness, mood disturbances, and sexual side effects. cOCPs are contraindicated in smokers, patients with migraines, patients with history of stroke or hypertension, and patients with personal or family history of thromboembolism, liver disease, or diabetes. When selecting contraception, these factors must be weighed in conjunction with cutaneous effects.[34,35]

Hirsutism

cOCPs have long been used to treat hirsutism but are approved by the FDA for this indication.[36-40] In pooled data, cOCPs were more effective than placebo in 34 women, with a mean FG score reduction

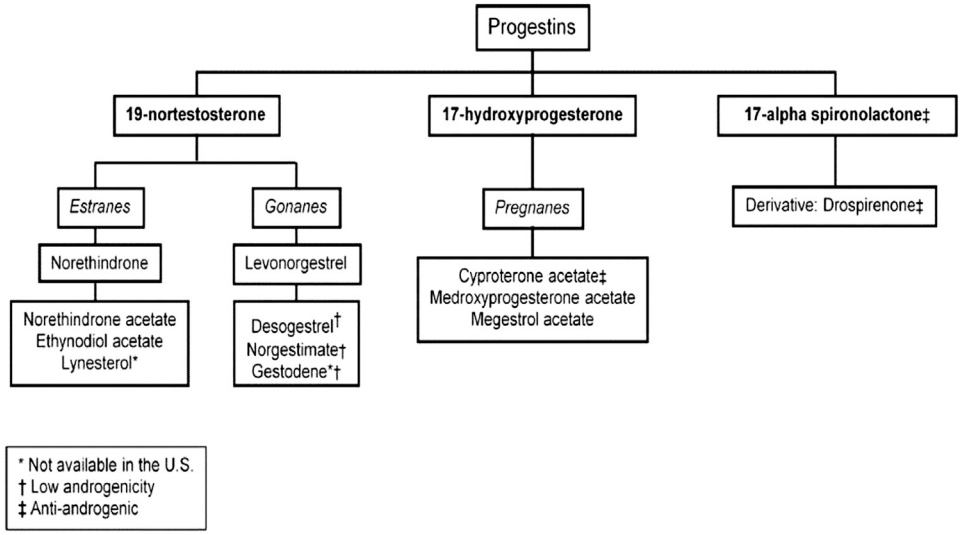

Fig 2. Classification of commonly used progestins. Adapted from Carr,[31] Grimes,[192] and Sitruk-Ware.[193,194]

of 8.[1,41,42] In 1 representative study, PCOS patients treated with desogestrel 15 μg/EE 30 μg had a FG score reduction from 16 to 8 over the first 9 months, with no significant decline after month 9.[43]

Limited data comparing older versus newer progestins have not shown differences in hirsutism effects. The study above found no difference in patients treated with desogestrel/EE and CPA 2 mg/EE 35 μg, an antiandrogenic cOCP.[43] Similarly, another study in hirsute women reported that desogestrel/EE was as effective as levonorgestrel 15 μg/EE 30 μg; free testosterone dropped significantly in the desogestrel group.[44,45]

Acne

cOCPs are typically effective for acne, but data for newer progestins are limited. In a Cochrane metaanalysis, cOCPs reduced inflammatory and noninflammatory facial lesion counts, severity grades, and self-assessed acne scores in 9 trials as compared with placebo.[46] However, data regarding cOCP differences in efficacy is difficult to interpret. In 4 trials comparing the older progestin levonorgestrel with the newer progestin desogestrel, 2 studies found no difference and 2 favored desogestrel—the latter including the largest study to date (n = 788) that also used a lower dose of EE.[47-50] A smaller study confirmed acne reduction,[51] and a review of cOCP effects on acne reported an inflammatory count decrease of 30% to 60% and symptom improvement in 50% to 90% of PCOS patients.[52] cOCP formulations that are approved by the FDA for acne include graduated EE with constant norethindrone acetate and norgestimate/EE preparations.

Metabolic factors

Although cOCPs are widely considered first-line therapy in PCOS, their use is controversial given the potential side effects. In addition to increasing risk of thromboembolism, stroke, myocardial infarction, and breast cancer, they may also increase insulin resistance, plasma lipids, and cardiac risk[27,53]; metabolic side effects may be greater with more androgenic progestins.[54-56] The current recommendations suggest low-dose cOCPs (<50 μg EE) to decrease cOCP-related diabetes risk. cOCPs also decrease low- and high-density lipoprotein and total cholesterol, but increase triglycerides, and should be avoided in women with hypertriglyceridemia.[57] Each patient's cardiometabolic risk profile should be evaluated before beginning therapy with cOCPs.[27] The addition of metformin may be useful in offsetting insulin resistance.[58]

COMBINED ORAL CONTRACEPTIVE PILLS WITH ANTIANDROGEN PROGESTINS

Key points

- **Antiandrogen progestin combined oral contraceptive pills include cyproterone acetate and drospirenone**
- **Drospirenone-containing combined oral contraceptive pills may increase risk of thromboembolism**
- **Careful consideration of cardiovascular risk factors, including age, should be given before prescribing drospirenone-containing combined oral contraceptive pills**

Cyproterone acetate

CPA 2 mg/EE 35 μg is used in Europe and Canada but is not approved by the FDA for use in the

United States. It is a steroidal antiandrogen (a 17-hydroxyprogesterone derivative) that competes with dihydrotestosterone for androgen receptor binding, inhibiting 5α-reductase activity. It also results in diminished testosterone and androstenedione production via negative feedback on the hypothalamic-pituitary axis and inhibiting luteinizing hormone secretion.[59] It has been extensively studied for both acne and hirsutism.

Drospirenone

Drospirenone has both anti-androgen and mineralocorticoid properties. Derived from spironolactone, drospirenone is available in the United States as drospirenone 3 mg/EE 30 μg, drospirenone 3 mg/EE 20 μg, and drospirenone 3 mg/EE 20 μg plus levomefolate calcium 451 μg. Drospirenone treats hyperandrogenism by blocking ovarian steroid production, reducing adrenal androgen synthesis and blocking peripheral androgen receptors in the dermis and pilosebaceous units.[40] Both drospirenone 3 mg/EE 20 μg and drospirenone 3 mg/EE 20 μg plus levomefolate calcium 451 μg are approved by the FDA for the treatment of moderate acne.

Only drospirenone/EE 20 μg and drospirenone/EE 20 μg plus levomefolate calcium 451 μg are approved by the FDA for the treatment of acne and premenstrual dysphoric disorder. Drospirenone/EE 30 μg is currently available in a generic version, which may be a financial consideration.

Risk of thromboembolism with combined oral contraceptive pills containing drospirenone and other progestins

It is well known that cOCPs increase venous thromboembolus (VTE) and pulmonary embolism risk, depending on type of progestin and dose of EE in the cOCP.[60] Relative to nonusers, levonorgestrel increases VTE risk 3.6-fold, gestodene 5.6-fold, desogestrel 7.3-fold, CPA 6.8-fold, and drospirenone 6.3-fold.[61] Observational studies report a 1- to 3-fold VTE increase when comparing drospirenone to levonorgestrel-containing cOCPs.[61-72] VTE often occurs in patients >35 years of age with at least 1 risk factor for thrombotic disease during the first year of treatment.[61,62,73,74] Although there is a known dose–response relationship between EE dosage and VTE events with cOCPs, especially with EE >50 μg,[75] recent studies in drospirenone-containing cOCPs suggest either no difference between EE 20 μg and 30 μg,[62] or even elevated risk with EE 20 μg compared with 30 μg.[76] There has been significant recent media discussion regarding VTE events in conjunction with drospirenone use. In April 2012, the FDA concluded that drospirenone-containing birth control pills may be associated with a higher risk for blood clots compared to other progestin-containing pills and added this information to package labels.[77]

However, absolute VTE risk of drospirenone-containing cOCPs (23-137 events/100,000 woman-years) is not much more than traditional levonorgestrel-containing cOCPs (6-92 events/100,000 woman-years), and comparatively, risk in pregnancy is much higher than both (<290 events/100,000 woman-years).[78,79] In PCOS patients with increased cardiovascular risk factors, it is important to weigh the risk:benefit ratio. In patients with additional risk factors, different medications should be explored. However, with careful consideration, providers can safely prescribe drospirenone-containing cOCPs.

Hirsutism

Small studies suggest that CPA is effective in PCOS for treating hirsutism and superior to placebo, desogestrel/EE, and drospirenone.[42,80-82] A Cochrane review determined that CPA improves hirsutism subjectively when compared to placebo, but is not more effective than ketoconazole, spironolactone, flutamide, finasteride, or gonadotropin-releasing hormone analogues.[59]

Although not approved by the FDA for the treatment of hirsutism, drospirenone may be highly effective. In 1 prospective study with 30 of 48 PCOS patients, drospirenone/EE 30 μg showed a mean decrease in FG score of 67% and 78% after 6 and 12 months, respectively, with the greatest improvement on the chest and abdomen, followed by the upper lip and chin.[40] Another study in PCOS found a 33% relative decrease in hirsutism when comparing drospirenone/EE 30 μg with desogestrel/EE, even 6 months after treatment discontinuation.[83]

Acne

Antiandrogen cOCPs are also effective for acne. Comparisons of CPA with dienogest 2 mg/EE 30 μg,[79] norgestimate 180 to 215 μg/EE 35 μg,[80] and drospirenone/EE 30 μg[84] have shown no significant differences.[46,85,86] Drospirenone/EE 30 or 20 μg may both be effective in treating acne in women with and without PCOS as compared with placebo.[87-90] One large randomized study showed a greater mean percentage change in total lesion count after 6 months of drospirenone/EE 30 μg compared to triphasic norgestimate 0.18/0.215/0.250 mg/EE 35 μg.[46,91]

NONORAL CONTRACEPTIVE ANTIANDROGENS: SPIRONOLACTONE, FINASTERIDE, AND FLUTAMIDE

Key points

- **Antiandrogen medications are helpful in treating hirsutism, with no clear difference in efficacy among agents**
- **All antiandrogens are harmful during pregnancy, and concomitant contraception must be emphasized with patients**
- **No antiandrogens are approved by the FDA for the treatment of acne or hirsutism**

Spironolactone

The aldosterone antagonist spironolactone shows dose-dependent competitive inhibition of the androgen receptor and inhibits 5α-reductase.[1,92] Of note, drospirenone 3 mg is approximately equivalent to CPA 1 mg and spironolactone 25 mg.[93] An 8-year study on spironolactone safety reported no serious complications; rare side effects include hyperkalemia, increased with adrenal, liver, or kidney disease.[94] Other side effects include menstrual irregularity (minimized by concurrent cOCP use), breast tenderness, and headaches. A recent cohort study found no increased risk of breast cancer with spironolactone.[94,95]

Finasteride

Finasteride is a progesterone-derived 5α-reductase inhibitor that blocks the conversion of testosterone to the potent androgen dihydrotestosterone.[96] The most commonly used dose is 5 mg per day, although studies suggest equal efficacy with 2.5 mg per day.[97] Common side effects include dry skin, libido reduction, and headaches.[98]

Flutamide

Flutamide is a potent nonsteroidal androgen antagonist used in prostate cancer treatment. The recommended dosing is 250 mg per day,[99] however, lower doses (125 or 62.5 mg/day) may have similar effects with fewer side effects.[100,101] Flutamide is rarely used because of its hepatotoxicity and high cost, although low doses (250 mg/day) may not be toxic in young and nonobese PCOS patients.[102]

All antiandrogenic agents may be harmful during pregnancy (spironolactone is pregnancy class C, finasteride class X, and flutamide class D). Therefore, we recommend concurrent contraception, when possible a cOCP.

Hirsutism

A metaanalysis comparing antiandrogens in hirsute women, some with PCOS, found all treatment groups had significantly lower hirsutism scores compared with placebo.[99,103-107] Studies suggest that antiandrogens alone, spironolactone/cOCP, metformin/cOCP, or flutamide/metformin combinations are all superior to cOCPs or metformin monotherapy.[108-110] A representative trial in 40 women, 21 with PCOS, comparing 6 months of spironolactone 100 mg per day, flutamide, or finasteride with placebo had a 40% FG score decrease in all treatment groups.[99]

Spironolactone is most commonly used for hirsutism in PCOS; studies have shown its efficacy specifically in this population.[111,112] A study exploring appropriate dosing found no difference between 100 and 200 mg per day.[113] Lower doses of spironolactone (25-50 mg/day) in combination with other therapies have also been efficacious in PCOS.[108,109]

Flutamide 250 mg twice daily may be more effective than finasteride when treating hirsutism in PCOS.[98,114] When added to a triphasic cOCP, flutamide may also be more effective for hirsutism and acne than cOCP/spironolactone 100 mg per day.[115]

Acne

Although a Cochrane review found that sample sizes were too small to determine spironolactone efficacy in treating acne,[113] studies have shown improvement with spironolactone 50 to 200 mg per day—but no studies have been conducted on women with PCOS.[116-119] In 85 patients, spironolactone 50 to 100 mg per day for 24 months demonstrated complete acne clearance in 33%, marked improvement in 33%, and partial improvement in 27%. Patients were undergoing spironolactone monotherapy or combination therapy with cOCPs, antibiotics, or both; subgroup analysis did not find a significant difference in any group.[118] In 27 patients, the addition of spironolactone 100 mg per day to drospirenone/EE 30 μg patients was efficacious, safe, and well tolerated.[120] Combination flutamide/cOCP improved acne by 80%, whereas spironolactone/cOCP improved acne by 50%.[115]

Alopecia

Antiandrogens have also been used to treat female pattern hair loss, although not studied specifically in PCOS. Spironolactone, finasteride, and CPA may have beneficial effects.[21,121-125] In 80 women treated with spironolactone 200 mg and CPA 50 or 100 mg per day, 44% experienced hair regrowth, measured by a visual clinical grading score. Results were not related to hormonal or menopausal status.[122]

INSULIN-SENSITIZING DRUGS

Key points

- **Because insulin-sensitizing drugs improve peripheral insulin sensitivity and decrease androgen production, they are often used as long-term treatment options for patients with polycystic ovary syndrome**
- **Metformin is the most widely used insulin-sensitizing drug, with the literature suggesting that it improves hirsutism, acne, and acanthosis nigricans**
- **Metformin may be more efficacious than antiandrogens for hirsutism, but comparisons to combined oral contraceptive pills are inconsistent**
- **The 2 thiazolidinediones available in the United States, rosiglitazone and pioglitazone, have improved hirsutism and acne in some studies, but have limited use because of cardiovascular side effects**

Metformin

Metformin increases peripheral glucose uptake, reduces intestinal glucose absorption, and is the most extensively studied insulin-sensitizing drug (ISD) for patients with PCOS.[126-129] However, because of its gastrointestinal side effects, it is not well tolerated and is often used second-line after spironolactone and is best reserved for patients with glucose intolerance, insulin resistance, or who are trying to conceive.

Many studies have explored metformin's effects in PCOS. With regard to hirsutism, several studies have noted FG score decreases with metformin compared with placebo,[130-138] while others have not.[127,139-147] Studies of metformin compared to or combined with cOCPs,[143,148-151] CPA,[134,152-154] and flutamide[7,143,147,148,155,156] are inconsistent. Metformin has been shown to be less effective than both flutamide and spironolactone in the treatment of hirsutism; however, the addition of flutamide was more effective than metformin alone.[107,148,157,158] A year-long comparison found a 25% FG score reduction with metformin compared with a 5% reduction with CPA[134,152]; however, in other studies, CPA decreased hirsutism more than metformin.[153,154]

Data for metformin regarding acne, androgenic alopecia, and acanthosis nigricans in patients with PCOS are inconsistent. Several trials have shown that metformin slightly improves acne in patients with PCOS[132,134,150,159]; others show that metformin is not effective for acne or androgenic alopecia.[126,134] In 1 study, 6 months of metformin reduced acanthosis nigricans but only minimally affected hirsutism and acne,[55,160] while another reported no impact on acanthosis nigricans.[147,161]

Thiazolidinediones

Thiazolidinediones (TZDs) suppress gluconeogenesis by increasing peripheral glucose uptake and decreasing hepatic glucose production.[129,162] Troglitazone was effective for hirsutism in patients with PCOS, but is no longer available because of hepatotoxicity.[148,155,156,163-165] Pioglitazone and rosiglitazone have different side effect profiles, but both have associated cardiovascular risks (rosiglitazone more) and hepatotoxicity.[127,166-168] They carry a black box warning for increased congestive heart failure risk and nonfatal myocardial infarction. In patients with PCOS who already have an increased cardiac risk, TZDs are second-line to metformin.

In PCOS, studies have shown that rosiglitazone and pioglitazone significantly decreased FG scores,[128,136,162,169-179] while others reported that neither medication improved hirsutism.[163,180-182]

TREATMENT RECOMMENDATIONS

Hirsutism

Data suggest that conventional cOCPs have fairly equivalent efficacy for hirsutism. We recommend first-line treatment with cOCPs containing low or antiandrogenic progestins, with appropriate consideration of small increased cardiometabolic risks of androgenic progestins (level of evidence IB; Table II). Data support the efficacy of drospirenone/EE 30 μg for hirsutism.[40,83] Trials show an effect on hirsutism beginning at 6 months; accordingly, we recommend 6 months of therapy before regimen modification.[1,183] Next, we recommend the addition of spironolactone when appropriate (level of evidence IA), beginning at 50 mg per day and increasing as needed, keeping in mind that drospirenone therapy accounts for 25 mg of spironolactone when the 2 medications are used together. cOCPs should be prescribed with spironolactone, whenever possible, to avoid teratogenicity and menstrual irregularities. We recommend checking the baseline potassium level, repeated after 1 month and after dose increases (level of evidence IV). We also suggest monitoring blood pressure while the patient is undergoing spironolactone therapy and checking for signs of hypotension, such as dizziness. Spironolactone should be avoided with angiotensin-converting enzyme inhibitors, high-dose nonsteroidal antiinflammatory drugs, or high potassium intake. If drospirenone-containing cOCPs are not prescribed because of a concern for VTE, spironolactone may be used with any cOCP for antiandrogen activity. We currently do not recommend flutamide or finasteride before spironolactone therapy.[99,115,184]

Table II. Treatment recommendations for the cutaneous manifestations of polycystic ovary syndrome

Cutaneous manifestation of PCOS	Treatment (level of evidence*)
Hirsutism	Lifestyle changes (III) Laser hair removal (IB) Minoxidil 1% or 5% (IB) Eflornithine hydrochloride 13.9% (IB) cOCPs containing low- or antiandrogenic progestins (IB) Addition of spironolactone (IA) Other antiandrogens: finasteride and flutamide (IA) Metformin (IB) Thiazolidinediones: pioglitazone and rosiglitazone (IB)
Acne†	Lifestyle changes (IV) cOCP containing low- or antiandrogenic progestins (IA) Addition of spironolactone (IB) Other antiandrogens: flutamide (IB) Metformin (III)
Alopecia	Antiandrogens: spironolactone and CPA (IIB) Antiandrogens: finasteride (III)

cOCP, Combined oral contraceptive pill; *CPA*, cyproterone acetate; *PCOS*, polycystic ovary syndrome.
*Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from at least 1 randomized controlled trial; level IIB evidence includes evidence from at least 1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies; level IV evidence includes evidence from opinions or clinical experience of respected authorities.
†After failing topical therapies.

Unfortunately, therapy withdrawal leads to hirsutism relapse. A study comparing spironolactone, desogestrel/EE, flutamide, and CPA reported that patients experienced mean FG score increases of 14.4 with no significant differences between groups 1 year after withdrawal.[185]

Acne

In patients who fail to respond to topical therapies, we recommend cOCPs with either low androgenicity or antiandrogenic properties as first-line therapy (level of evidence IA) over oral antibiotic therapy. With concurrent metabolic or cardiovascular risk factors, such as hypertension or elevated thromboembolism risk, we recommend working with the patient's internist or gynecologist to find the optimal cOCP that improves hyperandrogenism symptoms without negatively impacting cardiovascular risk.[57] There are currently no routine follow-up screening guidelines.[183]

After 3 months of insufficient treatment with a cOCP, we recommend the addition of spironolactone (level of evidence IB) starting at 50 mg per day. Small studies have shown 100 mg per day spironolactone is as effective as 200 mg per day and causes fewer side effects. Flutamide and finasteride data are insufficient to recommend their use.[115]

We do offer oral antibiotics as second-line therapy for short-term management and as adjunctive treatment when hormonal therapies alone are insufficient. Although there are no data comparing hormonal agents with oral antibiotic medications in patients with PCOS, 1 prospective study found isotretinoin effective in patients with PCOS; however, the relapse rate may have been slightly higher at 2 years posttherapy compared to patients without PCOS.[186] In patients whose acne is severe and refractory to oral antibiotics, oral contraceptives, and spironolactone, isotretinoin use should be considered.

In conclusion, given the absence of consistent evidence regarding the benefits of ISDs on acne or hirsutism, the literature weakly recommends metformin and TZDs.[96,145,152,176,187-190] Although metformin efficacy remains to be proven, it is safe; the efficacy and safety of TZDs remain questionable.[180,187] As a result, we typically do not use TZDs. Metformin, however, is useful in patients with glucose intolerance, insulin resistance, or who are trying to conceive; gastrointestinal side effects place it second-line to spironolactone. More longitudinal studies involving larger sample sizes, improved precision, and more aggressive investigations into treatment options are needed, including polytherapies where ISDs are coadministered with antiandrogen medications and/or cOCPs.

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Answers to CME examination

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