

What is optimal hormonal treatment for women with polycystic ovary syndrome?

In my practice, I commonly prescribe 3 hormone treatments for PCOS: combination estrogen-progestin contraceptive, metformin, and spironolactone. In combination, these medications rebalance the 3 system abnormalities commonly seen in women with PCOS, including reproductive, metabolic, and dermatologic dysfunction.



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Polycystic ovary syndrome (PCOS) is the triad of **oligo-ovulation** resulting in oligomenorrhea, **hyperandrogenism** and, often, **an excess number of small antral follicles** on high-resolution pelvic ultrasound. One meta-analysis reported that, in women of reproductive age, the prevalence of PCOS was 10% using the Rotterdam-European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) criteria¹ and 6% using the National Institutes of Health 1990 diagnostic criteria.² (See “The PCOS trinity—3 findings in one syndrome: oligo-ovulation, hyperandrogenism, and a multifollicular ovary” on page 12.)³

PCOS is caused by abnormalities in 3 systems: reproductive, metabolic, and dermatologic. Reproductive abnormalities commonly observed in women with PCOS include⁴:

- an increase in pituitary secretion of luteinizing hormone (LH), resulting from both an increase in

LH pulse amplitude and LH pulse frequency, suggesting a primary hypothalamic disorder

- an increase in ovarian secretion of androstenedione and testosterone due to stimulation by LH and possibly insulin
- oligo-ovulation with chronically low levels of progesterone that can result in endometrial hyperplasia
- ovulatory infertility.

Metabolic abnormalities commonly observed in women with PCOS include^{5,6}:

- insulin resistance and hyperinsulinemia
- excess adipose tissue in the liver
- excess visceral fat
- elevated adipokines
- obesity
- an increased prevalence of glucose intolerance and frank diabetes.

Dermatologic abnormalities commonly observed in women with PCOS include⁷:

- facial hirsutism
- acne
- androgenetic alopecia.

Given that PCOS is caused by abnormalities in the reproductive, metabolic, and dermatologic systems, it is appropriate to consider multimodal hormonal therapy that addresses all 3 problems. In my practice, I believe that the best approach to the long-term hormonal treatment of PCOS for many women is to prescribe a combination of 3 medicines: a combination estrogen-progestin oral contraceptive (COC), an insulin sensitizer, and an antiandrogen.

The COC reduces pituitary secretion of LH, decreases ovarian androgen production, and prevents the development of endometrial hyperplasia. When taken cyclically, the COC treatment also restores regular withdrawal uterine bleeding.

An insulin sensitizer, such as metformin or pioglitazone, helps to reduce insulin resistance, glucose intolerance, and hepatic adipose content, rebalancing central metabolism. It is important to include diet and exercise in the long-term treatment of PCOS, and I always

encourage these lifestyle changes. However, my patients usually report that they have tried multiple times to restrict dietary caloric intake and increase exercise and have been unable to rebalance their metabolism with these interventions alone. Of note, in the women with PCOS and a body mass index >35 kg/m², bariatric surgery, such as a sleeve gastrectomy, often results in marked improvement of their PCOS.⁸

The antiandrogen spironolactone provides effective treatment for the dermatologic problems of facial hirsutism and acne. Some COCs containing the progestins drospirenone, norgestimate, and norethindrone acetate are approved by the US Food and Drug Administration for the treatment of acne. A common approach I use in practice is to prescribe a COC, plus spironolactone 100 mg daily plus metformin extended-release 750 mg to 1,500 mg daily.

Which COCs have low androgenicity?

I believe that every COC is an effective treatment for PCOS, regardless of the androgenicity of the progestin in the contraceptive. However, some dermatologists believe that combination contraceptives containing progestins with low androgenicity, such as drospirenone, norgestimate, and desogestrel, are more likely to improve acne than contraceptives with an androgenic progestin such as levonorgestrel. In one study in which 2,147 women with acne were treated by one dermatologic practice, the percentage of women reporting that a birth control pill helped to improve their acne was 66% for pills containing drospirenone, 53% for pills containing norgestimate, 44% for pills containing desogestrel, 30% for pills containing norethindrone, and 25% for pills containing levonorgestrel.

In the same study, the percent of women reporting that a birth control pill made their acne worse was 3% for pills containing drospirenone, 6% for pills containing norgestimate, 2% for pills containing desogestrel, 8% for pills containing norethindrone, and 10% for pills containing levonorgestrel.⁹ Given these findings, when treating a woman with PCOS, I generally prescribe a contraceptive that does not contain levonorgestrel.

Why is a spironolactone dose of 100 mg a good choice for PCOS treatment?

Spironolactone, an antiandrogen and inhibitor of 5-alpha-reductase, is commonly prescribed for the treatment of hirsutism and acne at doses ranging from 50 mg to 200 mg daily.^{10,11} In my clinical experience, spironolactone at a dose of 200 mg daily commonly causes irregular and

bothersome uterine bleeding while spironolactone at a dose of 100 mg daily is seldom associated with irregular bleeding. I believe that spironolactone at a dose of 100 mg daily results in superior clinical efficacy than a 50-mg daily dose, although studies report that both doses are effective in the treatment of acne and hirsutism. Spironolactone should not be prescribed to women with renal failure because it can result in severe hyperkalemia. In a study of spironolactone safety in the treatment of acne, no adverse effects on the kidney, liver, or adrenal glands were reported over 8 years of use.¹²

What insulin sensitizers are useful in rebalancing the metabolic abnormalities observed with PCOS?

Diet and exercise are superb approaches to rebalancing metabolic



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The PCOS trinity—3 findings in one syndrome: oligo-ovulation, hyperandrogenism, and a multifollicular ovary

The two approaches most commonly used to diagnose polycystic ovary syndrome (PCOS) are the 1990 National Institutes of Health (NIH) criteria and the 2003 Rotterdam-European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) criteria (TABLE).^{1,2} In one meta-analysis, the prevalence of PCOS in women of reproductive age was 6% and 10% when using the NIH and ESHRE/ASRM criteria, respectively.³

TABLE Two diagnostic systems for identifying women with PCOS

1990 NIH Definition ¹	2003 Rotterdam-ESHRE/ASRM Definition ²
ALL REQUIRED	TWO OUT OF 3 REQUIRED
Hyperandrogenism (physical examination or laboratory testing)	Hyperandrogenism (physical examination or laboratory testing)
Oligo-ovulation, typically manifested as oligomenorrhea	Oligo-ovulation, typically manifested as oligomenorrhea
Exclude other hyperandrogenic disorders, including: nonclassical adrenal hyperplasia, ovarian tumors, Cushing syndrome, and hyperprolactinemia	Multifollicular morphology on ultrasonography (presence of ≥ 12 follicles in each ovary measuring 2 to 9 mm in diameter) or increased ovarian volume (>10 mL)

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abnormalities, but for many of my patients they are insufficient and treatment with an insulin sensitizer is warranted. The most commonly utilized insulin sensitizer for the treatment of PCOS is metformin because it is very inexpensive and has a low risk of serious adverse effects such as lactic acidosis. Metformin increases peripheral glucose uptake and reduces gastrointestinal glucose absorption. Insulin sensitizers also decrease visceral fat, a major source of adipokines. One major disadvantage of metformin is that at doses in the range of 1,500 mg to 2,250 mg it often causes gastrointestinal adverse effects such as borborygmi, nausea, abdominal discomfort, and loose stools.

Thiazolidinediones, including pioglitazone, have been reported to be effective in rebalancing central metabolism in women with PCOS. Pioglitazone carries a black box warning of an increased risk of

congestive heart failure and non-fatal myocardial infarction. Pioglitazone is also associated with a risk of hepatotoxicity. However, at the pioglitazone dose commonly used in the treatment of PCOS (7.5 mg daily), these serious adverse effects are rare. In practice, I initiate metformin at a dose of 750 mg daily using the extended-release formulation. I increase the metformin dose to 1,500 mg daily if the patient has no bothersome gastrointestinal symptoms on the lower dose. If the patient cannot tolerate metformin treatment because of adverse effects, I will use pioglitazone 7.5 mg daily.

Treatment of PCOS in women who are carriers of the Factor V Leiden mutation

The Factor V Leiden allele is associated with an increased risk of venous thromboembolism. Estrogen-progestin contraception is contraindicated

in women with the Factor V Leiden mutation. The prevalence of this mutation varies by race and ethnicity. It is present in about 5% of white, 2% of Hispanic, 1% of black, 1% of Native American, and 0.5% of Asian women. In women with PCOS who are known to be carriers of the mutation, dual therapy with metformin and spironolactone is highly effective.¹³⁻¹⁵ For these women I also offer a levonorgestrel IUD to provide contraception and reduce the risk of endometrial hyperplasia.

Combination triple medication treatment of PCOS

Optimal treatment of the reproductive, metabolic, and dermatologic problems associated with PCOS requires multimodal medications including an estrogen-progestin contraceptive, an antiandrogen, and an insulin sensitizer. In my practice, I initiate treatment of PCOS by

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offering patients 3 medications: a COC, spironolactone 100 mg daily, and metformin extended-release formulation 750 mg daily. Some patients elect dual medication therapy (COC plus spironolactone or COC plus metformin), but many patients select treatment with all 3 medications.

Although triple medication treatment of PCOS has not been tested in large randomized clinical trials, small trials report that triple medication treatment produces optimal improvement in the reproductive, metabolic, and dermatologic problems associated with PCOS.¹⁶⁻¹⁸ ●

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Dr. Barbieri reports no financial relationships relevant to this article.

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