

FIGURE Twelve or more follicles on this ovary indicate that polycystic ovary syndrome is likely. The diagnosis is confirmed if the patient has anovulation or oligo-ovulation or hyperandrogenism (hirsutism or elevated androstenedione and/or dehydroepiandrosterone sulfate levels).

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

Treating polycystic ovary syndrome: Start using dual medical therapy

➡ Many clinicians treat polycystic ovary syndrome with oral estrogen–progestin (OEP) monotherapy. Dual therapy with OEP plus metformin or OEP plus spironolactone is more effective.



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Using the Rotterdam criteria, the diagnosis of polycystic ovary syndrome (PCOS) is made in the presence of 2 of the following 3 criteria¹:

1. oligo-ovulation or anovulation
2. hyperandrogenism manifested by the presence of either hirsutism or elevated hormone levels (including serum testosterone androstenedione and/or dehydroepiandrosterone sulfate)
3. ultrasonography evidence of multifollicular ovaries (≥ 12 follicles with a diameter of 2 mm to 9 mm in one or both ovaries; **FIGURE**) or ovarian stromal volume of 10 mL or more.

Among reproductive-age women, the prevalence of PCOS has been reported to range from 8% to 13% for different populations.² Most clinicians initiate treatment for PCOS with oral estrogen–progestin (OEP) monotherapy. OEP treatment has many beneficial hormonal effects, including:

- a resulting decrease in pituitary luteinizing hormone (LH) secretion, which decreases ovarian androgen production
- an increase in liver production of

sex hormone–binding globulin (SHBG), which decreases free testosterone levels

- protection against the development of endometrial hyperplasia
- induction of regular uterine withdrawal bleeding.

However, OEP therapy neither improves metabolic indices (insulin sensitivity and visceral fat secretion of adipokines) nor blocks androgen action in the skin.

Dual medical treatment for PCOS can address the issues that monotherapy cannot and, along with providing guidance on improving diet and exercise, many experts support the initial therapy of PCOS with dual medical therapy (OEP plus metformin or spironolactone).

Advantages of OEP plus metformin

For many women with PCOS, the syndrome is characterized by abnormalities in both the reproductive (increase in LH secretion) and metabolic (insulin resistance and increased adipokines) systems. OEP monotherapy does not improve the

metabolic abnormalities of PCOS. Combination treatment with both OEP plus metformin, along with diet and exercise, can best treat these combined abnormalities.

Data support dual therapy with metformin. In one small, randomized trial in women with PCOS, OEP plus metformin (1,500 mg daily) resulted in a greater reduction in serum androstenedione and a greater increase in SHBG than OEP monotherapy.³ In addition, weight loss and a reduction in waist-to-hip ratio only occurred in the OEP plus metformin group.³ In another small randomized study in women with PCOS, OEP plus metformin (1,500 mg daily) resulted in a greater decrease in free androgen index than OEP monotherapy.⁴

In my clinical opinion, women who may best benefit from OEP plus metformin therapy have one of the following factors indicating the presence of insulin resistance⁵:

- body mass index >30 kg/m²
- waist-to-hip ratio ≥ 0.85
- waist circumference >35 in (89 cm)
- acanthosis nigricans
- personal history of gestational diabetes

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- family history of type 2 diabetes mellitus (T2DM) in a first-degree relative
- diagnosis of the metabolic syndrome.

My preferred treatment approach

Metformin is a low cost and safe treatment for metabolic dysfunction due to insulin resistance and excess adipokines. I often start PCOS treatment for my patients with an OEP plus metformin extended release (XR) 750 mg with dinner. If the patient tolerates this dose, I increase the dose to metformin XR 1,500 mg with dinner.

Adverse effects. The most common side effects of metformin are gastrointestinal, including abdominal discomfort, flatulence, borborygmi, diarrhea, and nausea. Metformin reduces serum vitamin B12 levels by 5% to 10%; therefore, ensuring adequate vitamin B12 intake (2.6 µg daily) is helpful.⁶ Although metformin does reduce vitamin B12 levels, there is no strong relationship between metformin and anemia or peripheral neuropathy.⁷ Lactic acidosis is a rare complication of metformin.

Beneficial effects. In the treatment of PCOS, metformin may have many beneficial effects, including⁸:

- decrease in insulin resistance
- decrease in harmful adipokines
- reduction in visceral fat
- reduction in the incidence of T2DM.

OEP plus spironolactone

Many women with PCOS have increased LH secretion and increased androgen activity in the skin due to increased 5- α reductase enzyme activity, which catalyzes the conversion of testosterone

Optimal dual therapy for PCOS when an OEP is contraindicated

An oral estrogen–progestin (OEP) may be contraindicated for the treatment of PCOS, for instance because of the presence of thrombophilia. In these cases, alternative dual therapy options include a progestin plus a second agent.

Options for progestin dual therapy include:

- oral norethindrone acetate 5 mg daily (which can lower luteinizing hormone levels and block ovulation) plus metformin
- norethindrone acetate 5 mg plus spironolactone
- levonorgestrel-intrauterine device plus metformin or spironolactone.

These progestin therapies reduce the risk of pregnancy and decrease the likelihood of endometrial hyperplasia development.

to the powerful intracellular androgen dihydrotestosterone.⁹ Women with PCOS may present with a chief problem report of hirsutism, acne, or female androgenetic alopecia. OEP plus spironolactone may be an optimal initial treatment for women with a dominant dermatologic manifestation of PCOS. OEP treatment results in a decrease in pituitary LH secretion and ovarian androgen production. Spironolactone adds to this therapeutic effect by blocking androgen action in the skin.

The data on dual therapy with spironolactone. Many dermatologists recommend spironolactone in combination with cosmetic measures for the treatment of acne, but there are only a few randomized trials that demonstrate its efficacy.¹⁰ In one trial spironolactone was demonstrated to be superior to placebo for the treatment of inflammatory acne.¹⁰ Authors of multiple randomized trials report that the antiandrogens, spironolactone, or finasteride are superior to metformin to treat hirsutism.¹¹ In addition, a few small trials report that spironolactone plus OEP is superior to either OEP or metformin monotherapy for hirsutism.¹¹ Clinical trials of spironolactone for hirsutism have been rated

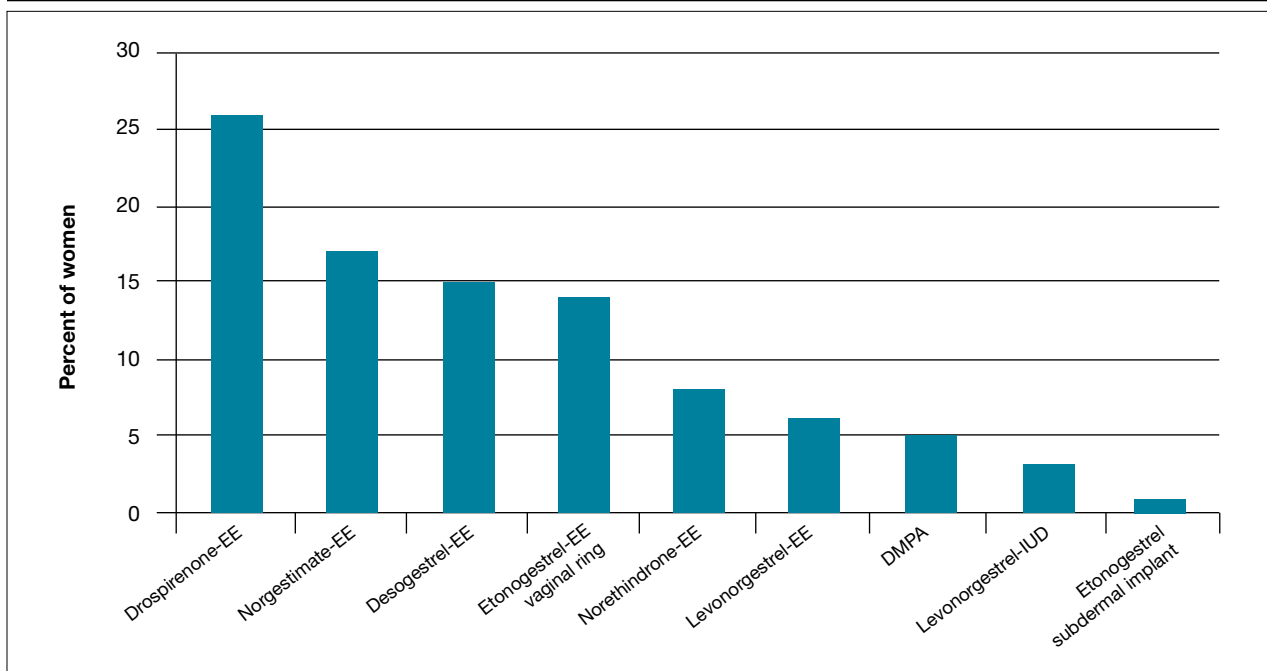
as “low quality” and additional controlled trials of OEP monotherapy versus OEP plus spironolactone are warranted.¹²

My preferred treatment approach

Spironolactone is effective in the treatment of hirsutism at doses ranging from 50 mg to 200 mg daily. I routinely use a dose of spironolactone 100 mg daily because this dose is near of the top of the dose-response curve and has few adverse effects (such as intermittent uterine bleeding or spotting). With spironolactone monotherapy at a dose of 200 mg, irregular uterine bleeding or spotting is common, but concomitant treatment with an OEP tends to minimize this side effect. In my practice I rarely have patients report irregular uterine bleeding or spotting with the combination treatment of an OEP and spironolactone 100 mg daily.

Contraindications. Spironolactone should not be given to women with renal insufficiency because it can cause hyperkalemia. However, it is not necessary to check potassium levels in young women taking spironolactone with normal creatinine levels.¹³

FIGURE Percentage of women reporting their contraceptive significantly improved their acne¹⁶



Abbreviations: DMPA, depot medroxyprogesterone acetate; EE, ethinyl estradiol; IUD, intrauterine device.

Triple therapy: OEP plus metformin plus spironolactone

Some experts strongly recommend the initial treatment of PCOS in adolescents and young women with triple therapy: OEP plus an insulin sensitizer plus an antiandrogen.¹⁴ This recommendation is based in part on the observation that OEP monotherapy may be associated with an increase in circulating adipokines and visceral fat mass as determined by dual-energy x-ray absorptiometry.¹⁵ By contrast, triple treatment with an OEP plus metformin plus an antiandrogen is associated with a decrease in circulating adipokines and visceral fat mass.

What is the best progestin for PCOS?

Any OEP is better than no OEP, regardless of the progestin used to treat the PCOS because ethinyl

estradiol plus any synthetic progestin suppresses pituitary secretion of LH and decreases ovarian androgen production. However, for the treatment of acne, using a progestin that is less androgenic may be beneficial.¹⁶

In one study, 2,147 consecutive women who were taking a contraceptive and presented for treatment of acne were asked if their contraceptive had a positive impact on their acne. The percentage of women reporting that their contraceptive significantly improved their acne ranged from 26% for those taking drospirenone-ethinyl estradiol (EE)

to 1% for those taking the etonogestrel subdermal implant (FIGURE).¹⁶ The US Food and Drug Administration has approved 4 OEP contraceptives for the treatment of acne (TABLE). The OEPs with drospirenone, norgestimate, desogestrel, or norethindrone acetate may be optimal choices for the treatment of acne caused by PCOS.


The bottom line

PCOS is a common endocrine disorder treated primarily by obstetricians-gynecologists. Among

TABLE FDA-approved estrogen-progestin contraceptives for the treatment of acne

Brand name	Generic name
Estrostep	Norethindrone acetate-ethinyl estradiol plus ferrous fumarate
Ortho Tri-Cyclen	Norgestimate-ethinyl estradiol
Yaz	Drospirenone-ethinyl estradiol
BeYaz	Drospirenone-ethinyl estradiol plus levomefolate

adolescents and young women with PCOS chief problem reports include irregular menses, hirsutism, obesity, acne, and infertility. Among mid-life women the presentation of PCOS often evolves into chronic medical problems, including obesity, metabolic syndrome, hyperlipidemia,

hypertension, T2DM, cardiovascular disease, and endometrial cancer.¹⁷⁻¹⁹ To optimally treat the multiple pathophysiologic disorders manifested in PCOS, I recommend initial dual medical therapy with an OEP plus metformin or an OEP plus spironolactone. 



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References

1. Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod.* 2004;19(1):41-47.
2. Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod.* 2016;31(12):2841-2855.
3. Elter K, Imir G, Durmusoglu F. Clinical, endocrine and metabolic effects of metformin added to ethinyl estradiol-cyproterone acetate in non-obese women with polycystic ovarian syndrome: a randomized controlled study. *Hum Reprod.* 2002;17(7):1729-1737.
4. Cibula D, Fanta M, Vrbikova J, et al. The effect of combination therapy with metformin and combined oral contraceptives (COC) versus COC alone on insulin sensitivity, hyperandrogenism, SHBG and lipids in PCOS patients. *Hum Reprod.* 2005;20(1):180-184.
5. Grundy SM, Brewer HB, Cleeman JJ, Smith SC Jr, Lenfant C; American Heart Association; National Heart, Lung, and Blood Institute. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation.* 2004;109(3):433-438.
6. Niafar M, Hai F, Porhomayon J, Nader ND. The role of metformin on vitamin B12 deficiency: a meta-analysis review. *Intern Emerg Med.* 2015;10(1):93-102.
7. de Groot-Kamphuis DM, van Dijk PR, Groenier KH, Houweling St, Bilo HJ, Kleefstra N. Vitamin B12 deficiency and the lack of its consequences in type 2 diabetes patients using metformin. *Neth J Med.* 2013;71(7):386-390.
8. Diamanti-Kandarakis E, Christakou CD, Kandarakis E, Economou FN. Metformin: an old medication of new fashion: evolving new molecular mechanisms and clinical implications in polycystic ovary syndrome. *Eur J Endocrinol.* 2010;162(2):193-212.
9. Skalpa P, Dabkowska-Huc A, Kazimierzczak W, Samojedny A, Samojedny MP, Chelmicki Z. Content of 5-alpha-reductase (type 1 and type 2) mRNA in dermal papillae from the lower abdominal region in women with hirsutism. *Clin Exp Dermatol.* 2006;31(4):564-570.
10. Layton AM, Eady EA, Whitehouse H, Del Rosso JQ, Fedorowicz Z, van Zuuren EJ. Oral spironolactone for acne vulgaris in adult females: a hybrid systematic review. *Am J Clin Dermatol.* 2017;18(2):169-191.
11. Swiglo BA, Cosma M, Flynn DN, et al. Clinical review: antiandrogens for the treatment of hirsutism: a systematic review and meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab.* 2008;93(4):1153-1160.
12. van Zuuren EJ, Fedorowicz Z. Interventions for hirsutism excluding laser and photoepilation therapy alone: abridged Cochrane systematic review including GRADE assessments. *Br J Dermatol.* 2016;175(1):45-61.
13. Plovianich M, Weng QY, Mostaghimi A. Low usefulness of potassium monitoring among healthy young women taking spironolactone for acne. *JAMA Dermatol.* 2015;151(9):941-944.
14. Ibanez L, de Zegher F. Low-dose combination of flutamide, metformin and an oral contraceptive for non-obese, young women with polycystic ovary syndrome. *Hum Reprod.* 2003;18(1):57-60.
15. Ibanez L, de Zegher F. Ethinyl estradiol-drospirenone, flutamide-metformin or both for adolescents and women with hyperinsulinemic hyperandrogenism: opposite effects on adipocytokines and body adiposity. *J Clin Endocrinol Metab.* 2004;89(4):1592-1597.
16. Lortscher D, Admani S, Stur N, Eichenfield LF. Hormonal contraceptives and acne: a retrospective analysis of 2147 patients. *J Drugs Dermatol.* 2016;15(6):670-674.
17. Wang ET, Calderon-Margalit R, Cedars MI, et al. Polycystic ovary syndrome and risk for long-term diabetes and dyslipidemia. *Obstet Gynecol.* 2011;117(1):6-13.
18. Joham AE, Ranasinha S, Zoungas S, Moran L, Teede HJ. Gestational diabetes and type 2 diabetes in reproductive aged women with polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2014;99(3):e447-e452.
19. Gottschau M, Kjaer SK, Jensen A, Munk C, Mellemkjaer L. Risk of cancer among women with polycystic ovary syndrome: a Danish cohort study. *Gynecol Oncol.* 2015;136(1):99-103.