

Drug Treatments for Polycystic Ovary Syndrome

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Polycystic ovary syndrome is a condition present in approximately 5 to 10 percent of women of childbearing age. Diagnosis can be difficult because the signs and symptoms can be subtle and varied. These may include hirsutism, infertility, menstrual irregularities, and biochemical abnormalities, most notably insulin resistance. Treatment should target specific manifestations and individualized patient goals. When choosing a treatment regimen, physicians must take into account comorbidities and the patient's desire for pregnancy. Lifestyle modifications should be used in addition to medical treatments for optimal results. Few agents have been approved by the U.S. Food and Drug Administration specifically for use in polycystic ovary syndrome, and several agents are contraindicated in pregnancy. Insulin-sensitizing agents are indicated for most women with polycystic ovary syndrome because they have positive effects on insulin resistance, menstrual irregularities, anovulation, hirsutism, and obesity. Metformin has the most data supporting its effectiveness. Rosiglitazone and pioglitazone are also effective for ameliorating hirsutism and insulin resistance. Metformin and clomiphene, alone or in combination, are first-line agents for ovulation induction. Insulin-sensitizing agents, oral contraceptives, spironolactone, and topical eflornithine can be used in patients with hirsutism. (*Am Fam Physician*. 2009;79(8):671-676. Copyright © 2009 American Academy of Family Physicians.)

► **Patient information:** A handout on polycystic ovary syndrome, written by the author of this article, is available at <http://www.aafp.org/afp/20090415/671-s1.html>.

Polycystic ovary syndrome (PCOS) is not a simple pathophysiologic process for which one treatment addresses all manifestations. It is a condition that occurs in approximately 5 to 10 percent of women of childbearing age.¹ It can affect women in many different ways; therefore, physicians must individualize treatment goals and target treatment to specific manifestations. Comorbidities (e.g., cardiovascular risk factors, endocrinologic disease) and the patient's desire for pregnancy must be considered when choosing a treatment regimen.

Diagnosis of PCOS may be difficult because the signs and symptoms can be subtle and varied. The most common manifestations include hirsutism, infertility, insulin resistance, and menstrual irregularities.² Physicians can diagnose PCOS when other causes of the symptoms or laboratory abnormalities are excluded; when oligo-ovulation or anovulation, usually manifested as oligomenorrhea or amenorrhea, is present; and when there is clinically confirmed hyperandrogenism (e.g., hirsutism, acne). Although the ovaries may be polycystic, this is usually not necessary for diagnosis. There is debate over which criteria should be used (e.g., 1990

National Institutes of Health criteria,³ 2003 Rotterdam consensus workshop criteria⁴). Guidelines suggest screening women with PCOS for other disorders, such as hyperlipidemia, and treating accordingly.⁵

Limitations of Data on Drug Treatment for PCOS

There have been many studies on PCOS in the past several years; however, most are fairly small. Also, many studies examine medication effects on surrogate markers (e.g., androgen levels) rather than clinical outcomes (e.g., hirsutism). The study results are often conflicting, and in a recent systematic review, only 33 of 115 possible studies met basic inclusion criteria (e.g., randomized controlled trials), suggesting that many of the data in the literature may have methodologic flaws.¹

One of the biggest challenges in reviewing the evidence for PCOS treatment is that many manifestations of the condition may be components of other disease processes. For example, there may be a study of medications that are useful for hirsutism, but the patient population in the study did not explicitly have PCOS. Thus, recommendations specific for treating symptoms of PCOS

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may be lacking. When reviewing a study of the treatment of insulin resistance in a general population, it cannot be assumed that the outcomes would mirror those in women with PCOS.

Insulin-sensitizing agents are indicated for most women with PCOS because they have positive effects on insulin resistance, menstrual irregularities, anovulation, hirsutism, and obesity. Of all the drugs used to treat manifestations of PCOS, metformin (Glucophage) has the most data supporting its effectiveness. *Table 1* details the most common medications used to treat manifestations of PCOS.⁶⁻²⁷

Medications for Manifestations of PCOS

HIRSUTISM

Treatments for hirsutism in women with PCOS are similar to those in women without PCOS, such as patients with idiopathic hirsutism. There are many nonpharmacologic treatment options, including electrolysis, waxing, bleaching, plucking, depilatory creams (a form of hair removal that dissolves the hair), thermolysis (use of heat), and laser therapy. Several medications have been studied for the treatment of hirsutism in women with PCOS. First-line agents include spironolactone (Aldactone)^{22,23,28-30} and metformin,^{13,16,20,22,31-33} as well as eflornithine (Vaniqa) for facial hirsutism.⁹

Combination oral contraceptives, especially those with progestins of norgestimate, desogestrel, or drospirenone (because of their low androgenic effects), are among the most commonly used medications for hirsutism in women with PCOS.² However, they are not approved by the U.S. Food and Drug Administration (FDA) for this use. One study found that women taking desogestrel/ethinyl estradiol (Apri) had lower hirsutism scores on a standardized scale (i.e., the Ferriman-Gallwey hirsutism score).³⁴ Finasteride (Propecia) and flutamide (formerly Eulexin) are effective, but are FDA pregnancy categories X and D, respectively; the use of these agents for hirsutism is strictly off-label.²

Because of its antiandrogenic effects, spironolactone is effective, but not FDA-approved, for this indication.^{22,23} A Cochrane review suggested that spironolactone is superior to finasteride.²⁸ Combining spironolactone with oral contraceptives may be synergistic, but caution should be used in women taking drospirenone because each agent can cause hyperkalemia.² Spironolactone is FDA pregnancy category C.

Insulin-sensitizing agents, including metformin,³¹ acarbose (Precose),²⁴ and rosiglitazone (Avandia),²⁰ may be used to treat hirsutism in women with PCOS. Spironolactone²² and rosiglitazone³² have been shown to

Table 1. Medications Used to Treat Manifestations of Polycystic Ovary Syndrome

Medication	Description
First-line	
Clomiphene (Clomid)†	Ovulation induction agent
Eflornithine (Vaniqa)‡	Inhibits hair growth
Metformin (Glucophage)§	Insulin-sensitizing agent
Oral contraceptives§	—
Pioglitazone (Actos)§	Insulin-sensitizing agent
Rosiglitazone (Avandia)§	Insulin-sensitizing agent
Spironolactone (Aldactone)§	Antiandrogenic antimineralocorticoid
Second-line	
Acarbose (Precose)§	Insulin-sensitizing agent
Desogestrel/ethinyl estradiol (Apri)§¶	Oral contraceptive
Finasteride (Propecia)§	5- α -reductase inhibitor
Flutamide (formerly Eulexin)§	Nonsteroidal antiandrogen used mostly in prostate cancer
Letrozole (Femara)§	Nonsteroidal competitive inhibitor of aromatase; inhibits conversion of adrenal androgens
Sibutramine (Meridia)§	Centrally acting appetite suppressant

CHF = congestive heart failure; FDA = U.S. Food and Drug Administration; GI = gastrointestinal; MI = myocardial infarction; PCOS = polycystic ovary syndrome.

*— Estimated monthly cost (unless otherwise noted) to the pharmacist based on average wholesale prices (rounded to the nearest dollar) in Red Book. Montvale, N.J.: Medical Economics Data; 2008. Cost to the patient will be higher, depending on prescription filling fee.

be more effective than metformin, based on Ferriman-Gallwey hirsutism scores. A Cochrane review suggested that metformin is as effective as oral contraceptives for treating hirsutism in women with PCOS,³³ but in contrast, a recent systematic review suggested that metformin is not effective.¹ Topical eflornithine cream is FDA-approved for management of unwanted facial hair, but there are no published data regarding its use

<i>Manifestations treated</i>	<i>FDA pregnancy category</i>	<i>Main adverse effects</i>	<i>Typical dosage</i>	<i>Approximate monthly cost*</i>
Infertility	X	Multiple pregnancy/ovarian hyperstimulation, thromboembolism, visual disturbances	50 to 100 mg per day ⁶⁻⁸	\$52 (generic) and \$128 (brand) for 100 mg per day for 5 days
Hirsutism	C	Mild skin irritation	13.9% cream applied to face twice per day ⁹	\$46 (brand) for one 30-g tube
Hirsutism; infertility; insulin resistance; menstrual irregularities	B	GI upset, lactic acidosis, increase in homocysteine levels	1,500 to 2,250 mg per day ¹⁰⁻¹⁶	\$73 (generic) and \$107 (brand) for 850 mg twice per day
Hirsutism; menstrual irregularities	X	Nausea, headache, spotting, thrombophlebitis, deep venous thrombosis	Varies	Varies
Hirsutism; infertility; insulin resistance	C	CHF, may cause weight gain	30 mg per day ^{14,17,18}	\$199 (brand)
Hirsutism; infertility; insulin resistance; menstrual irregularities	C	CHF, hepatotoxicity, edema, increase in homocysteine levels	2 to 8 mg per day (beneficial effects are dose related) ¹⁹⁻²¹	\$113 (brand) for 4 mg per day
Hirsutism; menstrual irregularities	C	Hyperkalemia, nausea, breast tenderness	50 mg per day to 100 to 200 mg per day ^{22,23}	\$61 (generic) and \$97 (brand) for 50 mg twice per day
Hirsutism; menstrual irregularities	B	GI upset	150 mg per day ²⁴ (for menses regulation)	\$94 (brand)
Hirsutism	X	Increased total cholesterol and low-density lipoprotein cholesterol; thromboembolism, stroke, MI	0.15 mg desogestrel plus 30 mcg ethinyl estradiol per day	\$31 (brand)
Hirsutism	X	Hypersensitivity reaction, decreased libido	5 mg per day ²⁵	\$148 (generic) and \$100 to \$343 (brand)
Hirsutism	D	Thrombocytopenia, leukopenia, liver toxicity, hot flashes	250 mg once or twice per day ²⁵	\$140 (generic) for 250 mg per day
Infertility	C	Osteoporosis, thromboembolism, MI, hot flashes, arthralgias	2.5 mg per day ⁶	\$340 (brand)
Hirsutism	C	Tachycardia, hypertension, headache, dry mouth	10 mg per day ²⁶	\$116 (brand)

†—FDA-approved for female infertility caused by PCOS.

‡—Not studied specifically in women with PCOS; therefore, effectiveness is unknown.

§—Not FDA-approved for treatment of manifestations of PCOS.²⁷

||—Based mostly on anecdotal evidence; cyproterone acetate plus ethinyl estradiol (drug not available in the United States) has been extensively studied.

¶—Studied in adolescents with PCOS.

Information from references 6 through 27.

specifically in women with PCOS. Sibutramine (Meridia), which is approved for obesity management, can also improve hirsutism.²⁶

INFERTILITY

Hormonal aberrations in women with PCOS (e.g., elevated androgen levels) can cause menstrual irregularities (e.g., oligomenorrhea, amenorrhea, anovulatory cycles)

that can lead to dysfunctional uterine bleeding and infertility.² First-line agents for ovulation induction and treatment of infertility in patients with PCOS include metformin^{8,11,15,32,35,36} and clomiphene (Clomid),^{6,7} alone or in combination, as well as rosiglitazone.^{19,20,32}

Clomiphene is an ovulation induction agent that has been used and studied in patients with and without PCOS.^{6-8,15,35,36} Studies have found that letrozole (Femara)

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>	<i>Comments</i>
First-line agents for the treatment of hirsutism in patients with PCOS include spironolactone (Aldactone) and metformin (Glucophage), as well as eflornithine (Vaniqa) for facial hirsutism.	A	9, 13, 16, 20, 22, 23, 28-33	Eflornithine is the only one of these agents that is approved by the U.S. Food and Drug Administration for facial hirsutism; however, it has not been studied specifically in women with PCOS.
First-line agents for ovulation induction and treatment of infertility in patients with PCOS include metformin and clomiphene (Clomid), alone or in combination, as well as rosiglitazone (Avandia).	A	6- 8, 11, 15, 19, 20, 32, 35, 36	—
Metformin improves insulin resistance (diagnosed by elevated fasting glucose or fasting glucose/insulin ratios) in patients with PCOS; other useful agents include rosiglitazone and pioglitazone (Actos).	C	10-21, 33, 37, 46, 47	There are ample studies supporting the effectiveness of metformin for improving insulin resistance; however, physicians should be aware that there are few patient-oriented outcomes regarding the importance of improving insulin resistance.
Metformin is probably the first-line agent for obesity or weight reduction in patients with PCOS.	B	10, 46, 49	—
Metformin can improve menstrual irregularities (e.g., oligomenorrhea) in patients with PCOS.	A	10, 11, 47, 51	—

PCOS = polycystic ovary syndrome.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort.xml>.

regulates ovulation and improves pregnancy rates in women with PCOS^{6,37,38}; however, this use is controversial because the drug is FDA pregnancy category D. It is embryotoxic and fetotoxic in animal studies, and there are no studies in pregnant women.

Insulin-sensitizing agents, including metformin,^{11,32} rosiglitazone,^{19,20,32} and pioglitazone (Actos),¹⁷ have been effective in improving fertility and ovulation in women with PCOS. There are contradictions in the literature regarding whether metformin, clomiphene, or a combination of the two agents is superior for improving pregnancy rates in women with PCOS. A 2003 Cochrane review suggested that metformin should be a first-line treatment for infertility in women with PCOS.³⁹ A more recent study confirmed that six months of metformin therapy was more effective than six months of clomiphene therapy for improving fertility in anovulatory, nonobese women with PCOS.⁸ However, a large randomized trial of more than 600 women found that clomiphene is superior to metformin in achieving live birth in infertile women with PCOS, with no statistical benefit to the addition of metformin to clomiphene.⁴⁰ Another study also showed no benefit from adding metformin to clomiphene.³⁵ However, two meta-analyses suggested that the combination is better than clomiphene alone.^{41,42} A more recent study found that, although ovulation rates were better with metformin than with clomiphene,

pregnancy rates were similar.⁴³ Finally, two systematic reviews found conflicting results; one suggests metformin does not affect ovulation or pregnancy rates,¹ and the other suggests it does.⁴⁴

INSULIN RESISTANCE

The prevalence of insulin resistance in women with PCOS, as measured by impaired glucose tolerance, is substantially higher than expected compared with age- and weight-matched populations of women without PCOS.⁴⁵ Although insulin resistance alone is a laboratory (not clinical) aberration, it can lead to diabetes, and it may be associated with the metabolic syndrome, thus leading to increased cardiovascular risk.² As with diabetes, optimal treatment of PCOS requires lifestyle modifications (e.g., diet, exercise) in addition to appropriate medications.

Metformin improves insulin resistance, as diagnosed by elevated fasting glucose or fasting glucose/insulin ratios, in patients with PCOS,^{10-16,46,47} and is probably the best agent to use. Women with PCOS who are not obese may benefit more from metformin than women who are obese.^{13,48} Metformin is FDA pregnancy category B.

Other insulin-sensitizing agents are also effective for improving insulin resistance in women with PCOS, including rosiglitazone¹⁹⁻²¹ and pioglitazone.^{14,17,18} However, these agents may cause or worsen congestive heart

failure, according to recent black box warnings,²⁷ or cause unwanted weight gain.

If a woman's weight is excessive, the physician should be aggressive in championing a weight-loss program. Medications effective for weight loss (in addition to lifestyle modifications) that have been specifically studied in women with PCOS include metformin, acarbose, sibutramine, and orlistat (Xenical). Metformin is probably the first-line medication for obesity or weight reduction in patients with PCOS. Metformin results in a decrease in body mass index (BMI) of 1 to 2 kg per m² or weight loss up to 6 lb, 10 oz to 8 lb, 13 oz (3 to 4 kg)^{10,46,49}; acarbose results in an approximate 3 kg per m² decrease in BMI²⁴; sibutramine results in a decrease in BMI of 5.8 kg per m² and weight loss of 31 lb, 11 oz (14.4 kg)²⁶; and orlistat results in weight loss of approximately 11 lb (5 kg).⁵⁰ However, a recent systematic review suggested that metformin is not effective for lowering BMI in patients with PCOS.¹

MENSTRUAL IRREGULARITIES

Anecdotally, oral contraceptives are among the most common agents used to treat menstrual irregularities in women with PCOS. However, there are few studies examining their effect on menstrual cycles in women with PCOS. Cyproterone acetate plus ethinyl estradiol has been extensively studied, but it is not available in the United States. Studies suggest that the following agents may improve menstrual irregularities (e.g., oligomenorrhea): spironolactone (in an open-label study),²² acarbose,²⁴ rosiglitazone,³² and metformin.^{10,11,32,47,51} Metformin is probably the best choice because it may improve insulin resistance in addition to improving menstrual irregularities.

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