

Polycystic Ovary Syndrome

A Review of Treatment Options With a Focus on Pharmacological Approaches

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a complex condition characterized by elevated androgen levels, menstrual irregularities, and/or small cysts on one or both ovaries.¹ The disorder can be morphological (polycystic ovaries) or predominantly biochemical (hyperandrogenemia). Hyperandrogenism, a clinical hallmark of PCOS, can cause inhibition of follicular development, microcysts in the ovaries, anovulation, and menstrual changes.²

PCOS is a heterogeneous disorder that affects at least 7% of adult women.³ According to the National Institutes of Health Office of Disease Prevention, PCOS affects approximately 5 million women of childbearing age in the U.S. Costs to the U.S. health care system for the identification and management of PCOS are approximately \$4 billion per year.⁴

Research suggests that 5% to 10% of females 18 to 44 years of age are affected by PCOS, making it the most common endocrine abnormality among women of reproductive age in the U.S.⁵ Women seeking help from health care professionals to resolve issues of obesity, acne, amenorrhea, excessive hair growth, and infertility often receive a diagnosis of PCOS. Women with PCOS have higher rates of endometrial cancer, cardiovascular disease, dyslipidemia, and type-2 diabetes mellitus.⁶ This article explores the pharmacotherapeutic management of PCOS.

ETIOLOGY

PCOS can be described as an oligogenic disorder in which the interaction of a number of genetic and environmental factors determine the heterogeneous, clinical, and biochemical phenotype.⁷ Although the genetic etiology of PCOS remains unknown, a family history of PCOS is relatively common; however, familial links to PCOS are unclear. A lack of phenotypic information prevents a formal segregation analysis. Nonetheless, the current literature suggests that the clustering of PCOS in families resembles an autosomal dominant pattern.⁸

Environmental factors implicated in PCOS (e.g., obesity) can be exacerbated by poor dietary choices and physical inactivity; infectious agents and toxins may also play a role.⁸ The reproductive and metabolic features of PCOS are sometimes reversible with lifestyle modifications such as weight loss and exercise.⁹

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PATHOPHYSIOLOGY

The pathophysiology of PCOS involves primary defects in the hypothalamic–pituitary axis, insulin secretion and action, and ovarian function.^{8,9} Although the cause of PCOS is unknown, PCOS has been linked to insulin resistance and obesity. The association with insulin function is expected; insulin helps to regulate ovarian function, and the ovaries respond to excess insulin by producing androgens, which can lead to anovulation.⁸ Follicular maturation arrest is a hallmark sign that an ovarian abnormality exists.

Clinical signs of PCOS include elevated luteinizing hormone (LH) and gonadotropin–releasing hormone (GnRH) levels, whereas follicular-stimulating hormone (FSH) levels are muted or unchanged. As a result of the increase in GnRH, stimulation of the ovarian thecal cells, in turn, produces more androgens.¹⁰ Follicular arrest can be corrected by elevating endogenous FSH levels or by providing exogenous FSH.⁹ Some studies suggest that PCOS is a primary defect in young girls who are entering puberty and who have a family history of the disorder. Approximately 25% of patients with PCOS have elevated prolactin levels.¹¹

Therapeutic interventions are designed to reduce insulin levels and ovarian androgen production, ultimately correcting sex hormone–binding globulin (SHBG) levels. This increase in SHBG levels can be used to effectively manage the symptoms of PCOS. Studies have reported that thecal cells in patients with PCOS produce higher amounts of testosterone, progesterone, and 17-hydroprogesterone than in normal patients. These cells have been altered in PCOS patients whose cytochrome P450 (CYP) *11A*, *3-HSD2*, and *CYP17* genes exhibit elevated levels.¹² Obesity is a common comorbidity of PCOS but is not required for diagnosis.

CLINICAL PRESENTATION

PCOS is a hormonal disorder with a potential to lead to various diseases. It also continues to be a common cause of infertility among women.⁵ Although signs and symptoms vary (Table 1), the three most common factors associated with PCOS include ovulation irregularities, increased androgen levels, and cystic ovaries.^{5,13} Problems with ovulation and elevated androgen levels occur in the majority of women with PCOS.¹³ Moreover, hirsutism, acne, and alopecia are directly associated with elevated androgen levels, and the prevalence of polycystic ovaries on pelvic ultrasound exceeds 70% in patients with PCOS.¹³

DIAGNOSIS

Three tools can be used to diagnose PCOS (Table 2). In 1990,

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Table 1 Signs and Symptoms of Polycystic Ovary Syndrome

Enlarged ovaries with numerous small cysts
Irregular menstrual cycles
Pelvic pain
Hirsutism
Alopecia
Acne
Acanthosis nigricans
Skin tags

the National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH) hosted a panel of experts who developed the first known criteria for PCOS.^{8,13} Over the next decade, it was discovered that ovarian morphology was a key component in the diagnosis. The European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) sponsored a workshop in Rotterdam. During the workshop, polycystic ovarian morphology on pelvic ultrasound was added to the NICHD/NIH criteria. It was then decided that only two of the three criteria had to be met for a diagnosis of PCOS.^{8,13}

In 2006, the Androgen Excess Society (AES) suggested that the NICHD/NIH criteria could be used with modifications that included the Rotterdam tool. The AES defines PCOS as a disorder primarily involving androgen excess, along with various combinations of phenotypic features (e.g., hyperandrogenemia, hirsutism, oligo-ovulation/anovulation, and/or polycystic ovaries) that may promote a more accurate diagnosis.^{8,13}

In 2012, the NIH sponsored an evidence-based methodology workshop on polycystic ovary disease. The expert panel concluded that each criterion has its own strengths and weaknesses; however, the use of multiple criteria was considered confusing, impeding progress in understanding PCOS.¹⁴

If PCOS is suspected, a complete medical history, physical examination, blood tests, and a pelvic ultrasound should be performed.⁵ A medical history and physical examination provide the physician with information about unexplained weight gain, menstrual cycle abnormalities, male-pattern hair growth, skin changes, and elevated blood pressure (BP). Blood is drawn to assess hormone, glucose, and lipid levels, and a pelvic ultrasound is performed to scan for ovarian cysts.^{5,13,15} During the assessment period, other potential causes associated with

reproductive, endocrine, and metabolic dysfunction should be excluded. Physicians should rule out adrenal hyperplasia, Cushing's syndrome, and hyperprolactinemia before a PCOS diagnosis is confirmed.^{5,13}

After PCOS is diagnosed, studies show that more than 50% of patients develop prediabetes or diabetes, and there is an increased risk of myocardial infarction (MI), dyslipidemia, hypertension, anxiety, depression, endometrial cancer, and sleep apnea.⁴ Moreover, pregnant women with PCOS should be informed of the increased rates of miscarriage, gestational diabetes, pre-eclampsia, and premature delivery.⁴

TREATMENT

Nonpharmacological Approaches

Because the primary cause of PCOS is unknown, treatment is directed at the symptoms. Few treatment approaches improve all aspects of the syndrome, and the patient's desire for fertility may prevent her from seeking treatment despite the presence of symptoms.¹⁶ Treatment goals should include correcting anovulation, inhibiting the action of androgens on target tissues, and reducing insulin resistance.

Weight reduction for obese patients with PCOS is beneficial in many ways. Weight loss helps to decrease androgen, luteinizing hormone (LH), and insulin levels. It also helps to regulate ovulation, thereby improving the potential for pregnancy.¹⁷

Laparoscopic ovarian drilling is an outpatient surgical intervention in which multiple perforations are created in the ovarian surface and stroma.¹⁸ It is thought that this intervention destroys androgen-producing tissue, which should lead to decreased androgen levels. It has been found to be as effective as medical interventions without increasing the risk of multiple pregnancies.

Pharmacological Approaches

Anovulation

Clomiphene. The drug of choice for inducing ovulation in PCOS is clomiphene citrate (Clomid, Sanofi), although the precise mechanism of action is unknown. Initially, a dose of 50 mg/day for 5 days is given. If ovulation occurs but no pregnancy results, 50 mg/day for 5 days is continued for the subsequent cycles. However, if ovulation does not occur after the first cycle, the dose may be increased to 100 mg daily for 5 days at least 30 days after the previous course of therapy.

Further treatment is not usually recommended after three courses of therapy; however, up to six cycles may be attempted before further therapy is considered. Clomiphene results in successful pregnancies approximately 30% of the time; however, 20% of these pregnancies result in spontaneous abortions or

Table 2 Diagnostic Tools for Polycystic Ovary Syndrome

NICHD/NIH Criteria (1990)	ESHRE/ASRM Rotterdam Criteria (2003)	Androgen Excess Society (AES) Criteria (2006)
<ul style="list-style-type: none"> Hyperandrogenism Oligo-ovulation/anovulation Exclusion of other related disorders 	<ul style="list-style-type: none"> Hyperandrogenism Oligo-ovulation/anovulation Polycystic ovaries 	<ul style="list-style-type: none"> Hyperandrogenism Oligo-ovulation/anovulation Polycystic ovaries Exclusion of other related disorders

Modified from criteria of the National Institute of Child Health and Human Development (NICHD)/National Institutes of Health (NIH)/European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM).

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stillbirths.¹⁹ Adverse effects may include ovarian enlargement; ovarian hyperstimulation syndrome (OHSS); multiple pregnancies; hot flashes; and gastrointestinal (GI) distention, bloating, and discomfort.

Antidiabetic agents. Other medications may be added to clomiphene to yield a more favorable outcome for ovulation. Antidiabetic drugs can be used to improve fertility, decrease insulin resistance, and reduce circulating androgen levels.

More data are available for metformin (Glucophage, Bristol-Myers Squibb) than for the thiazolidinediones in treating PCOS. The role of metformin for the treatment of infertility with PCOS was compared with placebo in a study that enrolled 320 women.²⁰ After 3 months of treatment with no resulting pregnancies, an appropriate infertility treatment was allowed to be added to the regimen for either group. Metformin, compared with placebo, was associated with significantly higher pregnancy rates (53.6% vs. 40.4%, respectively) and live birth rates (41.9% vs. 28.8%; respectively; $P = 0.014$) compared with placebo. However, in a meta-analysis in which the efficacy of metformin was evaluated in improving reproductive outcomes for women with PCOS, there was no evidence of improved rates of live births with metformin alone or in combination with clomiphene.²¹

A clomiphene/metformin combination may be tried if individual therapies fail, but evidence of improved results is limited. Clomiphene alone or in combination with metformin was compared with metformin alone in a randomized, double-blind trial.²² The clomiphene arm ($n = 209$) received 50 mg daily for 5 days beginning on day 3 of menses; this dose was titrated by 50 mg per cycle up to 150 mg. The metformin dose ($n = 208$) was titrated up to 1,000 mg twice daily, or a combination of both regimens was given ($n = 209$). Rates of live births were 22.5% in the clomiphene group, 7.2% in the metformin group, and 26.8% in the combination groups. In all, rates of live birth rates were significantly higher in the combination and clomiphene arms than in the metformin arm.

In a secondary analysis of these data, women with PCOS and elevated serum testosterone levels were randomly assigned to receive clomiphene alone or clomiphene with extended-release metformin ($n = 209$ in each group).²³ The overall prevalence of at least one ovulation after treatment was 75% and 83% ($P = 0.04$) for the clomiphene-only and clomiphene/metformin groups, respectively. Adding extended-release metformin does not reduce the dose of clomiphene required for the induction of ovulation in these patients. Metformin is generally well tolerated, although it is associated with initial GI disturbances, including diarrhea and nausea.

In a meta-analysis comparing pioglitazone (Actos, Eli Lilly) with metformin among patients with PCOS, pioglitazone was more effective in reducing fasting insulin levels and metformin was more effective in reducing body weight.²⁴

Gonadotropins. Human menopausal gonadotropin (HMG) and FSH can also be used to induce ovulation if clomiphene and/or metformin therapy fails. In one study of 302 women, 132 received low-dose FSH (50 units subcutaneously) on cycle day 4 with weekly incremental increases of 25 units, and 123 patients received clomiphene 50 mg for 5 days starting on day

4 with the dose titrated upward to 150 mg/day.²⁵ Pregnancy rates were higher with FSH than with clomiphene (58% vs. 44%, respectively; $P = 0.03$), and there were more live births with FSH (52% vs. 39%, respectively; $P = 0.04$).

Although gonadotropins might be more effective than clomiphene for inducing ovulation, the comparative expense and ease of administration of clomiphene favored clomiphene as a first-line therapy for fertility in PCOS. Of note, low-dose FSH was used in this study, because high doses are associated with an increased risk of multiple pregnancies and OHSS.²⁶

Aromatase inhibitors. Letrozole (Femara, Novartis) is an aromatase inhibitor approved for patients with hormone-responsive breast cancer, but it has also been studied for the induction of ovulation in PCOS. The difference between the efficacy of anastrozole (Arimidex, AstraZeneca) and letrozole was studied for ovulation induction; the difference in pregnancy rates was not considered statistically significant.²⁷

In a phase 2 dose-finding study, a 5-day regimen of various doses of anastrozole was compared with clomiphene 50 mg/day. Clomiphene resulted in higher rates of ovulation compared with all three doses of anastrozole.²⁸ Aromatase inhibitors may be considered for patients with clomiphene resistance or for women who are not candidates for clomiphene or gonadotropins because of the risk of congenital abnormalities associated with this class of medications.²⁹

Androgenic Symptoms

Cosmetic treatment of hirsutism, acne, and alopecia is an option for women dealing with the hyperandrogenic manifestations of PCOS. The use of depilatories, waxing, and shaving for managing hirsutism is limited by adverse effects such as skin redness and irritation. Other more expensive options may include medical spas that offer laser hair removal and electrolysis. Over-the-counter products can be used for acne, but they have limited effectiveness and are associated with treatment-site irritations. Alopecia can be treated topically or with oral antiandrogens.

Antiandrogens. Spironolactone (Aldactone, Pfizer), flutamide (Eulexin, Schering/Merck), and finasteride (Propecia, Merck) are antiandrogens that work in PCOS by decreasing androgen levels, thereby reducing the signs of hirsutism and acne. These antiandrogens may also improve lipid levels, which can be elevated in patients with PCOS. The effects of spironolactone 100 mg, flutamide 250 mg, and finasteride 5 mg daily were compared in 40 women with hirsutism for 6 months. All three drugs were found to be efficacious, although there was no significant difference between the groups.³⁰

Spironolactone, at a dose of 25 to 100 mg twice daily, is the most commonly used antiandrogen because of its safety, availability, and low cost. Because of the increased risk of teratogenicity to the male fetus (opposing genital formation), contraception is recommended when patients are using antiandrogens for the treatment of PCOS.³¹

Oral contraceptives. Women with PCOS who do not wish to become pregnant may consider oral contraceptives (OCs). The mechanism of action for OCs in the treatment of PCOS is

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primarily through the regulation of menstrual periods. These drugs also reduce hirsutism, acne, and androgen levels. Estrogen and progestin combinations are the primary OCs used in the treatment of hirsutism and acne associated with PCOS.

Although data are sparse, some newer OCs contain antiandrogenic progestins, such as Bayer's drospirenone (e.g., Yaz) and dienogest (e.g., Natazia). Theoretically, these drugs are more effective for treating androgenic symptoms compared with older formulations. Women with hirsutism usually notice clinical improvement after approximately 6 months of treatment with OCs.³² The data also suggest that OCs can be combined with antiandrogens for synergy.³³

Other Therapies

Medroxyprogesterone acetate. In a dosage regimen of 5 to 10 mg/day for 10 to 14 days each month, medroxyprogesterone acetate (MPA) can be used to treat amenorrhea or dysfunctional uterine bleeding in women with PCOS who do not wish to conceive and who are not at risk for pregnancy. Monthly progestin therapy obviates abnormal endometrial proliferation but does not suppress ovarian androgen production.¹³ MPA may also improve insulin sensitivity and lipid profiles in patients with PCOS.³⁴⁻³⁶

Statins. Statins are considered to have a place in the treatment of PCOS because of their ability to reduce testosterone levels, as well as low-density lipoprotein-cholesterol (LDL-C), triglycerides, and total cholesterol.³⁷ In a comparison of simvastatin (Zocor, Merck) and metformin in women with PCOS, total testosterone levels were reduced by 17.1% and 13.6%, respectively.³⁸ Simvastatin had a superior effect compared with metformin alone, but the combination was not found to be superior to simvastatin alone, at 15.1%.

CONCLUSION

Polycystic ovary syndrome is a complex disorder for which multiple treatment approaches are required, depending on the reason a patient seeks treatment. Clomiphene has shown the best results in treating infertility, whereas data are limited regarding the pharmacological treatment of androgenic symptoms. Long-term consequences of PCOS, which include type-2 diabetes and cardiovascular disease, can be treated with antidiabetic drugs and statins.

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