

Polycystic Ovarian Syndrome Management Options

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KEYWORDS

- Polycystic ovarian syndrome • Clomiphene citrate • Metformin
- Ovarian dysfunction

KEY POINTS

- The diagnosis of polycystic ovarian syndrome (PCOS) requires hyperandrogenemia, hirsutism, and/or polycystic ovarian morphology.
- Lifestyle modifications with structured exercise and diet programs are key to reducing the metabolic and reproductive dysfunction associated with PCOS.
- Metformin is the first-line agent for glucose intolerance associated with PCOS and may play a role as an adjunct to ovulation induction therapies.
- Clomiphene citrate (CC) remains the first line for oral ovulation induction. Letrozole's potential role in ovulation induction for women with PCOS seems promising but awaits definite data.
- Injectable gonadotropins increase the potential for ovulation but require intensive monitoring to avoid higher-order multiple pregnancies and ovarian hyperstimulation syndrome.
- Ovarian drilling should be reserved for women who fail medical management.
- Careful attention to health maintenance with assessment of cardiovascular and cancer risk is required in this patient population.

INTRODUCTION

Stein and Leventhal¹ are often credited with publishing the first article describing PCOS in 1935. Since their description of women with ovarian enlargement and absence of menses more 80 years ago, PCOS has garnered considerable attention and now may be the most common endocrine disorder, affecting up to 15% of all reproductive-aged women, depending on the diagnostic criteria used.² The

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reproductive sequelae of PCOS reflect ovarian dysfunction with the failure of antral follicles to develop into mature follicles. The cardinal signs of PCOS are enlarged ovaries with multiple small ovarian follicles and hyperandrogenism, often associated with hirsutism and metabolic syndrome. Obesity and glucose intolerance are common components of the PCOS clinical picture. Although there is no definitive laboratory test to confirm PCOS, the current consensus is to use a combination of symptoms and signs to diagnose PCOS.

DIAGNOSIS

PCOS spans a wide spectrum of reproductive and metabolic disorders. Women with PCOS may present with scant facial hair and irregular menses in an otherwise healthy state or have profound effects, such as absent menses, a full beard, severe insulin resistance, and morbid obesity, often seen with the hyperandrogenism, insulin resistance, and acanthosis nigricans syndrome.³ This heterogeneity adds to the controversy surrounding the diagnosis of this syndrome. More than 2 decades ago, the National Institutes of Health convened a consensus conference to develop formal diagnostic criteria for PCOS.⁴ The original criteria included

- Clinical or biochemical evidence of hyperandrogenism
- Chronic anovulation
- Exclusion of other known disorders

These criteria were updated by the Rotterdam European Society of Human Reproduction and Embryology (ESHRE)/American Society for Reproductive Medicine (ASRM) PCOS consensus workshop group.^{5,6} This gathering concluded that PCOS is a syndrome of ovarian dysfunction along with the cardinal features of hyperandrogenism and polycystic ovary (PCO) morphology. The Rotterdam criteria are the most commonly used guidelines for the diagnosis of PCOS and require 3 of the following 4:

- Irregular or absent ovulation defined as 8 or fewer menstrual cycles per year
- Clinical (hirsutism) or biochemical (raised serum testosterone levels) signs of androgen excess
- Polycystic-appearing ovaries with 12 or more antral follicles ranging in size from 2 mm to 9 mm and increased ovarian volume of at least 10 mL³ (**Fig. 1**)

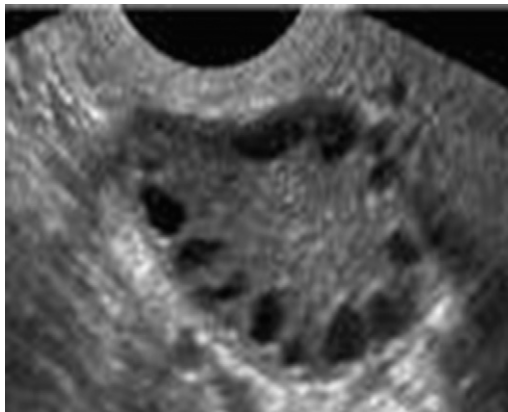


Fig. 1. Polycystic Ovarian Morphology.

AND

- Exclusion of other causes, including congenital adrenal hyperplasia (CAH), androgen-secreting tumors, and Cushing syndrome

Conversely, the Androgen Excess and PCOS Society states that PCOS should be first and foremost viewed as a syndrome of androgen excess.⁷ They stress that PCOS is not a specific disease but a syndrome with a group or collection of signs (physical findings) and symptoms (patient complaints) that suggest a common disorder. Their diagnostic criteria include

- Hyperandrogenism with hirsutism and/or elevated free testosterone

AND

- Ovarian dysfunction with oligoanovulation and/or polycystic ovaries

AND

- Exclusion of other androgen excess or related disorders

The slight variability among these diagnostic criteria allow for many clinical presentations. It has been estimated that up to 10 distinct phenotypes are possible based on the different combinations of the 4 clinical symptoms: hyperandrogenemia, hirsutism, menstrual dysfunction, and polycystic ovarian morphology.⁷

Polycystic ovarian morphology provides the namesake of this condition and can be visualized on transvaginal ultrasound in the majority of women with this syndrome. Most experts argue, however, that the presence of polycystic ovaries in the absence of androgen excess and ovarian dysfunction does not warrant the diagnosis of PCOS. Women with marked elevation of androgens or rapid onset of clinical symptoms may require imaging to screen for an androgen secreting neoplasm. Transvaginal ultrasound assessment of the endometrial cavity may be warranted in some women with PCOS to detect uterine hyperplasia or cancer.

Before the diagnosis of PCOS is made, other endocrine disorders should be considered. All anovulatory patients should be screened for hypothyroidism and hyperprolactinemia. In the presence of acne, hirsutism, or virilization, testing for androgen excess should be done. In PCOS, a normal to mildly elevated level of androgens is expected; however, excessive levels of testosterone or dehydroepiandrosterone sulfate (DHEAS) could indicate an androgen-producing tumor in the adrenal gland or ovary.

Clinically, it can be difficult to distinguish PCO from CAH because they both can have hirsutism and anovulation. CAH is usually caused by 21-hydroxylase deficiency. The screening test for CAH is 17-OH progesterone, which is elevated in CAH.

Cushing syndrome, a rare disorder with an incidence of 10 to 15 people per million, may also present with menstrual regularities and infertility.⁸ The highest risk groups are patients with poorly controlled diabetes, hypertension, and early-onset osteoporosis. Testing is recommended in patients with multiple symptoms and signs of Cushing syndrome, including a round (or moon) face, buffalo hump on the back of the neck, abdominal obesity, and abdominal striae. Patients with Cushing syndrome usually have hypertension and glucose intolerance. The syndrome is caused by chronic exposure to excess glucocorticoids. A 24-hour urine cortisol or overnight dexamethasone suppression test is the preferred screening test for Cushing syndrome. Cushing disease refers to one specific cause of Cushing syndrome, a tumor in the pituitary gland that produces large amounts of corticotropin, which in turn elevates cortisol.

CLINICAL PRESENTATION

Women with PCOS present with a wide range of symptoms. The most common are menstrual irregularities⁷; 80% of women have menstrual irregularities, ranging from the more common oligomenorrhea to the less common amenorrhea. Oligomenorrhea usually results from anovulatory estrogen breakthrough bleeding after a prolonged period without ovulation to produce endogenous progesterone. Most women with PCOS have polycystic ovaries on ultrasound (75%–90%) and biochemical or clinical signs of androgen excess (70%). The androgen excess is manifested by hirsutism (60%–75%) and, more rarely, male pattern balding. Women with PCOS are commonly obese (65%–75%) and also frequently have insulin resistance (50%–70%). PCOS is also one of the most frequently seen causes of infertility and the most common cause of ovulatory dysfunction, present in 70% of women with ovulatory dysfunction.⁹

There is considerable overlap between PCOS and the metabolic syndrome but the two are not synonymous. The metabolic syndrome is present, however, in 30% to 40% of the women with PCOS and many of the individual components (truncal obesity, hypertension, and hyperlipidemia) are even more common.¹⁰ Many of the metabolic manifestations of PCOS can be attributed to hyperinsulinemia.¹¹ Insulin resistance in tissues leads overproduction of insulin and results in hyperinsulinemia. This hyperinsulinemia is not purely related to obesity because women with PCOS are more likely to have insulin resistance than weight-matched controls. Hyperinsulinemia act on the liver to suppress sex hormone-binding globulin (SHBG) production. As SHBG is decreased, the levels of circulating free androgens increases. Not only does hyperinsulinemia decrease SHBG but it also stimulates pituitary luteinizing hormone (LH) production, which increases androgen production by the ovaries (**Fig. 2**). Researchers continue to explore the pathophysiologic mechanism underlying the spectrum of disease seen with PCOS, but the reproductive and metabolic dysfunction associated with this syndrome warrants a comprehensive approach.

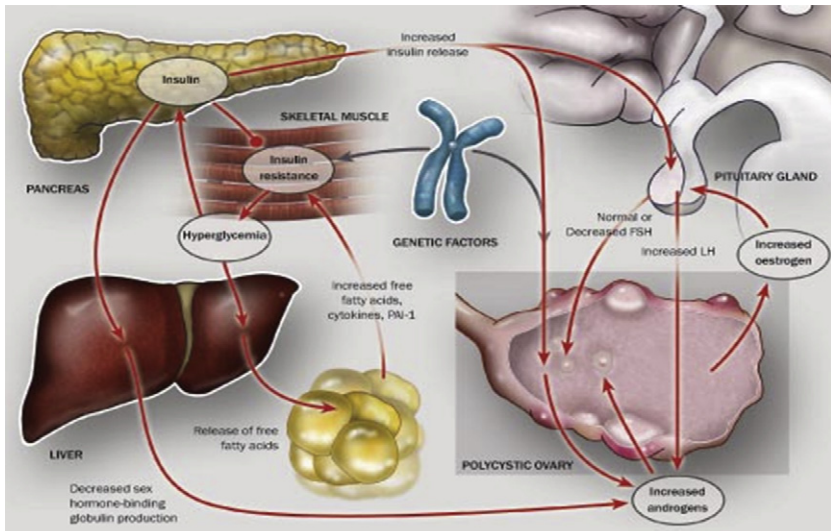


Fig. 2. Polycystic Ovarian Syndrome Pathophysiology. (Adapted from Nestler JE. Metformin for the treatment of the polycystic ovary syndrome. *N Engl J Med* 2008;358(1):47–54).

TREATMENT OPTIONS

Lifestyle Modification

Among women with PCOS, 65% to 75% are obese. Obesity has a significant impact on reproductive outcome. When a woman's body mass index (BMI) is greater than 35, the time to conception is increased 2-fold to 4-fold. Obesity not only influences time to conception but also adversely affects the response to fertility treatment. It also plays a role in adverse pregnancy outcomes once pregnant. There is an increased risk of miscarriage, congenital anomalies, and third-trimester pregnancy complications, in particular, preeclampsia and stillbirth.¹² Women should be provided with assistance to lose weight, including psychological support, dietary advice, exercise classes, and, where appropriate, weight-reducing agents or bariatric surgery.

The recommended first line of treatment is weight loss. Randomized control trials have found that weight loss strategies that use in-person support or remote support (telephone, e-mail, Web site) are more effective in achieving and sustaining clinically significant weight loss than patients whose weight loss is self-directed.¹³ Studies have also shown that women with PCOS who initiate lifestyle changes with dietary changes, physical activity, and behavioral advice have lower levels of hirsutism, hyperandrogenism, weight and waist circumference, and insulin resistance.¹⁴ A study evaluating patients with PCOS doing a structured exercise program averaging 92 minutes per week reported an average 5% reduction in BMI and 60% resumption of normal menses.¹⁵ Palomba and colleagues¹⁶ examined structured exercise programs compared with hypocaloric hyperprotein diets in women with PCOS and found the group that had a structured exercise program had significantly higher frequency of ovulation and spontaneous menses. Both the exercise group and the diet group had significantly lower weights, BMI, waist circumference, insulin resistance indexes, and serum levels of SHBG, androstenedione, and DHEAS compared with baseline. They also found that patients with PCOS who failed to ovulate when given 100 mg of CC for 5 days (CC resistant), had significantly higher rates of ovulation when given CC after 2 weeks of a structured exercise program and low caloric diet, compared with those who did not change their diet or exercise.¹⁷

Medical Management of PCOS

Weight loss

A wide array of complementary alternative medicines and prescription drugs have been proposed to combat the obesity and metabolic dysfunction associated with PCOS. Although acupuncture may be viewed as a surgical intervention, some investigators have suggested that it reduces hyperandrogenism and improves menstrual frequency in PCOS.¹⁸ Americans also spend millions of dollars on diet aids despite few data on their efficacy. A recent systematic review concluded that nonprescription dietary supplements as an adjunct to weight loss currently cannot be strongly recommended.¹⁹ Prescription weight loss medications also suffer from nebulous efficacy data and often concerning side-effect profiles. The only therapy currently Food and Drug Administration approved for the long-term management of obesity, orlistat, may be effective for the glucose intolerance associated with PCOS because it has been shown to reduce BMI and the progression to type 2 diabetes mellitus. Its use is limited, however, by gastrointestinal side effects.²⁰ Recent data support the use of phentermine/topiramate in obese and overweight adults. This drug combination has been shown to reduce weight, decrease cardiovascular risk factors, and improve metabolic function when used in conjunction with lifestyle modification.²¹ These medications, however, have not been adequately assessed in women with PCOS and should be avoided in anyone pursuing fertility.

Hormonal suppression

Many women who do not desire fertility present to their health care provider complaining of the menstrual irregularity, hirsutism, or acne associated with PCOS. Oral contraceptives (OCPs) are the first-line therapy for most of these women. In addition to menstrual cycle regulation, OCPs reduce LH-mediated androgen production and decrease the biologic activity of androgens by increasing SHBG. Antiandrogens, including spironolactone, flutamide, and finasteride, have equivalent efficacy for hirsutism but have not been shown to augment the benefit seen with OCPs. New hair growth may also be reduced with topical therapy, eflornithine hydrochloride.²² Despite the availability of many agents to combat excess hair growth, removal techniques, including laser and electrolysis, are preferable in many circumstances.

The Amsterdam ESHRE/ASRM-sponsored third PCOS consensus workshop group summary recommendation for the medical management of symptoms associated with androgen excess and PCOS included

- The benefits of OCPs outweigh the risks in most patients with PCOS and subsequent fertility is not reduced.
- There is no evidence for differences in effectiveness for contraception and hirsutism or risks among the various progestogens and when used in combination with a 20-mg versus a 30-mg daily dose of estrogen.
- Prolonged (>6 months) medical therapy for hirsutism is necessary to document effectiveness.
- Antiandrogens should not be used without effective contraception.
- Flutamide is of limited value because of its dose-dependent hepatotoxicity.

Ovulation induction

PCOS is the most common cause of ovulatory dysfunction and one of the most frequently seen identifiable causes of infertility. CC is the most common initial oral ovulation induction medication. CC is taken 3 to 5 days after the onset of a spontaneous or progestin induced menses.²³ Treatment typically begins with a single 50-mg tablet daily for 5-day and is increased by 50 mg up to 250 mg a day in subsequent months if ovulation cannot be confirmed. Most conceptions occur within the first 6 ovulatory cycles and at doses of less than 150 mg a day but the fecundity rate decreases dramatically with age (<4% at >41 years of age).^{24,25} Letrozole is an aromatase inhibitor that is used off label for ovulation induction in women who fail to conceive with CC. Letrozole is typically prescribed at a starting dose of 2.5 mg to 5 mg and can be increased by increments of 2.5 mg but the optimum dose range has not been established.²⁶ Letrozole may have a better side-effect profile and result in fewer multiple pregnancies. Definitive data regarding efficacy and unsubstantiated concerns for potential birth defects limit its adoption as a first-line agent. Ovulation induction is discussed at length in the article by Propst elsewhere in this issue.

Metformin

Metformin is a biguanide antihyperglycemic agent approved for the treatment of type 2 diabetes mellitus. It decreases blood glucose levels by suppressing hepatic glucose levels, decreasing intestinal absorption of glucose, and enhancing the peripheral glucose uptake and use.²⁷ When used in anovulatory women with PCOS, it acts to decrease insulin levels and LH. As the levels of insulin and LH are decreased, the level of SHBG increases. Ultimately, the levels of androgens are decreased, in part because of the increased level of SHBG but also because LH decreases. Women with PCOS also benefit from metformin because it typically causes a slight reduction in

weight.^{28–30} One study showed a 16% reduction in weight, resulting in a 200% increase in glucose clearance in women taking metformin.³¹

Studies have found that approximately 50% of women with PCOS or anovulatory cycles resume regular menses after taking metformin for 6 months. This is also true in adolescents with PCOS; many resume regular menses 4 to 6 months after initiating therapy with metformin.²⁷

The target dose of metformin, in anovulatory patients, is typically 1500 mg to 2500 mg. The most common side effects are gastrointestinal in nature and include diarrhea, nausea, emesis, flatulence, indigestion, and abdominal discomfort. The reported discontinuation rate is 5% secondary to side effects.²⁷ Metformin XL or the liquid formulation typically has fewer side effects.³² Metformin is excreted by the kidney and can be linked to lactic acidosis in women with renal insufficiency or liver dysfunction. It should be temporarily suspended before surgery or radiologic procedures that use intravenous (IV) contrast.²⁷

Metformin is a category B drug for pregnancy. The preliminary studies of women with PCO who continue metformin in pregnancy show that it may lower the incidence of first trimester losses and reduce the development of gestational diabetes. There have been no documented adverse effects on birth weight, growth, or motor development through 18 months of development.^{33,34}

Metformin and clomiphene citrate

The combination of metformin and CC seems to have an additive effect in some anovulatory women. In Nestler and colleagues' landmark study, 60 PCOS women with a mean BMI of 32.3 were randomized to metformin (500 mg 3 times daily) versus placebo.³⁵ Women who did not ovulate on metformin or placebo were given CC 50 mg days 5 to 9; 90% of the obese, PCOS women who received metformin plus CC ovulated whereas 8% of the women who received CC plus placebo ovulated.

Metformin has also been compared head-to-head with CC for ovulation induction in anovulatory women with PCOS. In an Italian study of women with PCOS and a BMI less than 30, the incidence of ovulation with CC or metformin was examined.³⁶ The rates of ovulation were similar between the 2 groups, at approximately 65%. The pregnancy rates (PRs) were higher, however, in the metformin arm at (70%) compared with CC arm (34%), whereas the miscarriage rates were higher in the CC arm. This study first suggested that metformin may be a better first-line treatment of ovulation induction for women with PCOS.

A more comprehensive, multicenter National Institutes of Health–sponsored study looked at the live birth rates (LBRs) in more than 600 women with PCOS and oligoovulation or anovulation who were randomized to up to 6 months of treatment with CC alone, metformin alone, or a combination of CC and metformin.³⁷ The LBR was 22.5% in the CC group, 7.2% in the metformin group, and 26.8% in the group receiving metformin and CC. The LBR was significantly higher in women taking either CC alone or in the combination group, confirming that CC is a superior first-line treatment for anovulatory women with PCOS.

A recent meta-analysis of 14 prospective trials also showed a reduction in the LBR in the group of patients treated with metformin as a first-line agent when compared with CC alone (odds ratio [OR]= 0.48; 95% CI, 0.31–0.73; $P = .0006$). It also found an increase in ovulation (OR 1.6; 95% CI, 1.2–2.1; $P = .0009$) and PR (OR 1.3; 95% CI, 1.0–1.6; $P = .05$) in patients treated with a combination of CC and metformin compared with CC alone, but no difference was found when LBR was analyzed (OR 1.1; 95% CI, 0.8–1.5; $P = .61$).³⁸

A 3-month course of metformin before initiating infertility treatment, however, seems to improve LBRs when compared with a placebo. A recently published multicenter trial in Finland randomized 320 women with PCOS and anovulatory infertility equally to metformin (BMI ≥ 27 mg/m² received 2000 mg daily; BMI < 27 mg/m² received 1500 mg daily) or placebo.³⁹ After 3 months' treatment, another appropriate infertility treatment was combined if necessary. Intent-to-treat analysis showed that metformin significantly improved PR and LBR (vs placebo) in the whole study population (PR 53.6 vs 40.4%, $P = .006$; LBR 41.9 vs 28.8%, $P = .014$) and PR in women with a BMI greater than or equal to 27 mg/m² (49.0 vs 31.4%, $P = .04$) with a trend toward improved LBR (35.7 vs 21.9%, $P = 0.07$). Cox regression analysis showed that metformin plus standard infertility treatment increased the chance of pregnancy 1.6 times (95% CI, 1.13–2.27). In summary, women with a BMI greater than or equal to 27 mg/m² especially seem to benefit from 3 months' pretreatment with metformin before initiating ovulation induction and this can be combined with lifestyle changes in women who are trying to lose weight.

Surgical Management of PCOS

Before the availability of ovulation induction agent, surgical intervention was the gold standard for the treatment of PCOS. The enlarged polycystic ovaries were initially believed the cause of the androgen excess and reproductive dysfunction and, thus, amenable to surgical intervention. Removal of a wedge of the ovarian by laparotomy often resulted in restoration of ovulation in 8 of 10 women and PRs that exceeded 50%. The improvements in ovarian function, however, were often temporary and fertility potential reduced by adhesion formation.⁴⁰ The development of minimally invasive surgery, including laparoscopy, has led to a resurgence of interest in the surgical interventions for PCOS.

Laparoscopic ovarian diathermy (LOD) is a contemporary version of the Stein-Leventhal ovarian wedge resection for PCOS. It is a laparoscopic procedure in which electrocautery or laser is used to create focal areas of damage in the ovarian cortex to reduce circulating and intraovarian androgen levels and reduce the volume of ovarian stroma. Approximately 4 to 20 areas of damage are created. It has the most success in women with a BMI less than 30 and an LH of greater than 10.

LOD is recommended by expert consensus as a second-line intervention, as are gonadotropins, in women with PCOS who are CC resistant.⁴¹ The use of exogenous gonadotropins is associated with increased risk for a multiple pregnancy and requires intense monitoring of ovarian response. LOD is a good choice for those women for whom gonadotropin therapy is not practical due to long distances from a fertility specialist or those patients who have economic or religious concerns with using gonadotropins. LOD alone is usually effective in less than 50% of women and additional ovulation induction medication is required when the surgery itself does not result in spontaneous ovulation.^{41,42}

LOD has been compared with CC as a first-line intervention and found less effective in a randomized clinical trial.⁴² There is a risk of adhesions or ovarian damage after ovarian diathermy. LOD has also been compared with metformin in women with PCOS who did not ovulate with CC treatment.⁴³ This randomized controlled trial looked at ovulation, pregnancy, miscarriage, and LBRs between the two groups. The rates of ovulation after LOD or metformin (850 mg twice a day) were not statistically different. The PRs (18.6% vs 13.4%), miscarriage rates (15.4% vs 29%), and LBRs (82.1% vs 64.5%) were statistically better in the metformin group.

A recent Cochrane review evaluated 9 trials involving LOD, including 1210 women.²² Live births were reported in 34% of women in the LOD group and 38% in the medically

treated groups, including CC, letrozole, and gonadotropins. The LOD group had significantly fewer live births (OR 0.44; 95% CI, 0.03–0.52; $P = .004$) compared with the CC plus metformin subgroup. The rate of multiple pregnancies was significantly lower in the LOD group compared with trial using gonadotropins (OR 0.13; 95% CI, 0.03–0.52; $P = .04$).

HEALTH MAINTENANCE

Patients with PCOS are at risk for metabolic syndrome, diabetes, or cardiovascular disease and it is imperative that health care providers perform appropriate screening. The Androgen Excess and PCOS Society states that risk-category women with PCOS who also display obesity (especially abdominal adiposity), cigarette smoking, hypertension, dyslipidemia (increased low-density lipoprotein cholesterol [LDL-C] and/or non-high-density lipoprotein cholesterol [HDL-C]), subclinical vascular disease, insulin or glucose intolerance, and a family history of premature CVD (<55 years of age in male relative or <65 years of age in female relative) undergo the following screening:

- Blood pressure, waist circumference, and BMI at every visit
- Lipid profile (total cholesterol, LDL-C, non-HDL-C, HDL-C, and triglycerides) every 2 years
- 2-Hour post-75-g oral glucose challenge performed with a BMI greater than 30 kg/m² or, alternatively, in lean PCOS women with advanced age (>40 years), personal history of gestational diabetes, or family history of type 2 diabetes mellitus

The 3rd PCOS consensus workshop group recommended CVD risk assessment at any age for psychosocial stress, blood pressure, glucose, lipid profile (cholesterol, triglycerides, HDL, LDL, and non-HDL-C), waist circumference, physical activity, nutrition, and smoking.²

Screening for depression, anxiety, and quality of life⁴⁴ as well as sleep apnea⁴⁵ has also been suggested. Menstrual irregularity and obesity may also warrant heightened surveillance with endometrial biopsy or uterine ultrasound for endometrial cancer in women with PCOS.

SUMMARY RECOMMENDATIONS

- Lifestyle modifications with diet and exercise with weight loss are key to the successful management of both the reproductive and metabolic dysfunction seen in association with PCOS.
- Metformin, 1500 mg to 2500 mg daily, may be used in conjunction with CC in women with PCOS who do not ovulate when using CC alone. It is less efficient when used alone compared with CC for ovulation induction but may be beneficial when initiated alone for 3 months in overweight and obese women who are trying to lose weight before starting ovulation induction medications.
- Oral ovulation agents are the first-line treatment for ovulatory infertility seen with PCOS.
- Injectable gonadotropins may result in higher-order multiples and, thus, require thoughtful consideration of the risk/benefit profile with careful monitoring.
- LOD is a second-line intervention that is less effective than the combination of CC and metformin. It may be indicated for patients who fail to ovulate with oral agents for whom gonadotropins are a poor choice due to distance from fertility specialists or concern about a multiple pregnancy.

- Routine health maintenance and proper screening for metabolic syndrome, diabetes, and cardiovascular disease are crucial in the proper care of women with PCOS.

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