

REVIEW

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Polycystic Ovary Syndrome: Update on Treatment Options and Treatment Considerations for the Future

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Abstract: Polycystic ovary syndrome is an endocrine disorder characterized by insulin resistance, hyperandrogenemia, obesity, and inflammation, and is the most common cause of infertility. Women with PCOS are at higher risk than non-PCOS women for diabetes, cardiovascular disease, endometrial cancer, and psychiatric disorders. Because many abnormalities present in PCOS and symptoms vary considerably among PCOS women, treatment is guided by presentation and does not consist of simply one modality. Often, however, one type of medication can ameliorate more than one abnormality in PCOS. This review summarizes current research on several treatment modalities for PCOS, including drugs that are fairly well-established as efficacious and other agents that may prove efficacious in the future, with particular emphasis on the benefits and barriers of lifestyle change.

Keywords: polycystic ovary syndrome, medical treatment, lifestyle change, self-determination theory, barriers

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Polycystic ovary syndrome (PCOS) is defined by chronic anovulation or oligo-ovulation, hyperandrogenism, and polycystic ovaries and occurs in 8%–17% of women.^{1,2} Women with PCOS often present with infertility, obesity, and clinical features of hyperandrogenism, such as hirsutism, acne, and alopecia. Women with PCOS are at greater risk than non-PCOS women for insulin resistance and associated diseases (eg, diabetes, cardiovascular disease), endometrial cancer, and psychiatric problems such as depression and anxiety disorders.

Treatment for PCOS generally follows a multi-pronged, biopsychosocial approach depending upon the medical needs and desires of the patient. A single treatment modality, however, usually ameliorates more than one abnormality in PCOS. For example, metformin, a biguanide insulin sensitizer, can be prescribed to combat insulin resistance and improve fertility. Another common medication, the oral contraceptive (OC) pill, improves hirsutism and acne and may reduce the risk of developing endometrial cancer.

Lifestyle change in the form of healthier diet and/or increased physical activity improves menstrual and metabolic abnormalities and reduces androgen levels. In fact, weight loss via lifestyle change often is the first line of treatment for PCOS due to its wide range of benefits, and even a small amount of weight loss can improve several parameters in PCOS, namely fertility. Additionally, lifestyle change as first-line treatment for PCOS is advantageous because, compared with medication prescription or medical procedures, it generally is not accompanied by unpleasant side effects and does not add to the sky-rocketing cost of health care.

The purpose of this paper is to summarize current treatment strategies for PCOS and those that show promise of being potential treatment modalities in the future. Particular attention is paid to the impact of lifestyle change on PCOS parameters and especially to lifestyle change barriers, which may in and of themselves be important to address while treating a woman with PCOS.

Lifestyle Change

It is well-known that obesity is more common among women with PCOS compared with the general population and that women with PCOS are more likely than

non-PCOS women to develop diabetes, cardiovascular disease, endometrial cancer, and other medical problems that are due partly to obesity. Conversely, PCOS and its clinical features are more common in women who are overweight and obese compared to those of normal weight.^{3,4} Obesity adversely impacts birth rate response to treatments for infertility, including ovarian electrocautery,⁵ clomiphene citrate (CC), and metformin.⁶

Modest weight loss (5%–10% of initial body weight) can improve nearly all abnormal reproductive, metabolic, hormonal, lipid profile, and psychological parameters in women with PCOS.^{7–17} Furthermore, exercise interventions improve insulin resistance and restore menstrual cycles regardless of weight change,^{18–20} suggesting that many aspects of a lifestyle intervention can improve outcomes.

With regard to diet, clearly any diet that results in weight loss will be beneficial to a woman with PCOS, but given the likelihood of insulin resistance, one could speculate that low-carbohydrate and/or low-glycemic index diets may be especially effective. Indeed, studies have demonstrated that low-carbohydrate diets and/or low-glycemic diets among overweight/obese PCOS women result in significant reductions in body weight, fat mass, free testosterone, LH/FSH ratio, free androgen index, and insulin resistance; and improvements in lipid profile and menstrual cyclicity compared with relatively higher-carbohydrate diets.^{14,21–24} In some cases, improvements in metabolic and clinical outcomes occurred independently of weight loss.²³

Lifestyle modification, especially in obese women with PCOS, indeed has become a primary focus of treatment, called for by numerous researchers and the Androgen Excess PCOS Society.⁷ Especially in light of the ways that metabolic, pro-inflammatory, hormonal, behavioral, and psychological abnormalities common in PCOS interact to exacerbate clinical outcomes and disorders (ie, infertility, diabetes, endometrial cancer, cardiovascular disease, depression), many researchers are approaching treatment of PCOS from a biopsychosocial perspective and emphasizing the importance of behavioral intervention.^{16,25–28} Additionally, it seems prudent to note that, in light of burdensome health care costs, successful lifestyle change and weight loss may reduce the need for prescription medication and medical procedures.²⁹



Despite well-known benefits of weight loss and increased physical activity, especially among women with PCOS, the attrition rate in lifestyle intervention studies is quite high. For example, in a PCOS sample, 49% of participants dropped out of a study comparing a low-glycemic index diet to a conventional healthy diet²³ with no difference in attrition between the groups. Another study comparing a high protein diet to low protein diet among women with PCOS reported a 38% attrition rate,¹⁴ while studies in PCOS women comparing a diet intervention to exercise intervention report attrition rates of 45%⁸ and 35%,¹⁹ also with no differences between groups regarding attrition. In one study among obese and overweight women comparing a lifestyle intervention (diet + exercise) to metformin and placebo, attrition rates among the 3 groups were marginally significantly different ($P = 0.08$) with the highest attrition in the lifestyle intervention group.³⁰ In another study comparing metformin to placebo among women with PCOS, 67% of participants dropped out by the end of the 6-month trial with no difference in attrition between groups.³¹

These researchers reported that many of the drop-outs were lost to follow-up and therefore their reason for attrition is unknown, but some participants did cite family and work commitments as reasons for attrition. Marsh et al²³ noted that drop-outs tended to be heavier and more insulin resistant; it may be that those who are obese have difficulty changing their lifestyles. Potential inhibitory body image and self-esteem issues aside, biological differences between women with PCOS and controls may account for some of this difficulty. For example, women with PCOS may have a lower basal metabolism and lower postprandial thermogenesis compared to controls,^{32,33} but these results are not consistently found.^{34,35} Appetite regulation may also interfere with diet compliance, as it has been reported (albeit inconsistently) that ghrelin and cholecystokinin may be decreased in women with PCOS.^{36–38} Thus, one could speculate that a woman with PCOS may need to put forth more effort with regard to physical activity and caloric restriction than a non-PCOS woman in order to lose weight.

Some women may resort to bariatric surgery in order to achieve weight loss. Several studies have found that bariatric surgery resulted not only

in significant weight loss but also improvements in menstrual cyclicity in PCOS and non-PCOS women,^{39,40} and insulin resistance, hyperandrogenism and its clinical signs, and pregnancy rates among women with PCOS.⁴¹ Thus, in the severely obese PCOS woman, bariatric surgery may be an option, especially if other treatments fail to improve reproductive and/or metabolic parameters, but more research is needed in this area.

Barriers to Lifestyle Change

Given extensive public awareness of both the increasing prevalence of obesity and its adverse effects (particularly in PCOS) and the benefits of lifestyle change, one must wonder why women with PCOS do not commit to lifestyle change on their own or to research studies that provide information on and (financial or other) incentive for lifestyle change. One could argue that the attrition rate of such studies is a noteworthy result in and of itself. The Androgen Excess and Polycystic Ovary Syndrome Society has posited that issues of intervention compliance and weight maintenance are ripe for research investigation.⁷ A review paper by Moran and colleagues²⁶ concluded that further research is warranted in order to determine an intervention among women with PCOS that will maximize compliance. More broadly, of course, the general population in America continues to become increasingly obese despite extensive media coverage touting the health dangers of obesity.

This evidence begs the question: what are barriers to lifestyle change? Perhaps psychological problems, such as depression, interfere with behavior change in women with PCOS, as is the case in persons with diabetes⁴² and heart failure.⁴³ It is now widely acknowledged that women with PCOS are at increased risk and should be assessed for several psychological problems such as depression and other mood disorders, anxiety disorders, poor body image and self-esteem, and worsened quality of life.^{44,45}

Some studies have shown that depression may affect compliance with lifestyle change among obese individuals. For example, a review paper concluded that long-term weight loss success is associated with a low (versus high) degree of depression,⁴⁶ and another study found that ever being diagnosed with depression was inversely related to degree of body mass index loss 4 years after bariatric surgery.⁴⁷ Among women



with PCOS, a recent study reported that inactive women are more likely to be mildly depressed,⁴⁸ but this association was correlational, so a causal relationship between depression and inactivity cannot be established. It may be that depression could inhibit an individual from seeking medical advice, as a very large study of infertile (>12 months without spontaneous conception) women aged 28–33 found that self-reported depression was associated with refraining from seeking medical advice to treat infertility.⁴⁹

If depression or other psychiatric disorders do interfere with lifestyle change, does psychiatric treatment affect lifestyle change? A systematic review of psychological interventions among overweight and obese individuals that employed mostly cognitive-behavioral techniques in addition to diet and exercise recommendations concluded that such therapeutic strategies were effective in losing weight.^{50,51} Many of these studies, however, were short-term, and Moran and colleagues²⁶ assert that the challenge of developing strategies that prevent or facilitate long-term weight loss remains.

What does motivate individuals to lose weight and adopt a healthier lifestyle for the long-term? Several studies have concluded that common reasons for weight loss include concerns about health, wishing to change one's physical appearance, and having a medical condition.^{52–55} Kalarchian et al⁵⁶ conducted a very interesting study with 203 overweight or obese women 18–55 years old who had endorsed that primary reasons for weight loss were to improve general health and physical appearance. They were randomly assigned to one of four treatment groups that emphasized either health or appearance concerns related to weight loss or a combination of the two concern areas plus a control group. Treatment sessions were conducted weekly for 24 weeks, followed by 6 months of monthly follow-up sessions. Women in the groups that emphasized concerns about appearance (either alone or in addition to concerns about health) lost significantly more weight than the control group over the course of a year. The group intervention that focused on health concerns did not demonstrate significantly better weight loss than the control group. These somewhat surprising results suggest that desire to improve one's appearance may be a motivation for weight loss.

It is possible that dissatisfaction with weight loss or unnoticeable changes in appearance could account

for some of the high attrition rates seen in lifestyle intervention studies, as weight loss is not immediate and often is disappointing in the face of perhaps unrealistic expectations.⁵⁵ Long-term weight loss studies frequently show that study participants regain much of the weight lost early on in the treatment,⁵⁷ but there is evidence that satisfaction *per se* with one's weight, appearance, body size/shape, and health may not be related to weight over the course of a year.⁵⁶

Another psychological concept at play that may motivate one to adopt a healthier lifestyle is risk perception about future diseases. It may be worthwhile, then, to assess a PCOS woman's risk perception of potential future disorders such as diabetes, infertility, endometrial cancer, and cardiovascular disease. One study included young women ages 18–25 with PCOS and an average BMI of 29.17 along with age-matched controls in a study assessing their perception of risk of several disorders common in PCOS.⁵⁸ They found that women with PCOS were significantly more likely than controls to perceive themselves at risk for obesity and infertility, but not for metabolic syndrome, diabetes, or cardiovascular disease, although they did endorse a greater importance to reduce risk for these disorders compared to controls. Whether an understanding of the importance to reduce risk is sufficient to lead to lifestyle change, however, is unknown. Likely the answer to this notion is “no,” or at least “not yet,” as researchers and clinicians continue to devise ways to assist the PCOS woman in weight loss. Furthermore, the national rate of obesity continues to climb despite increased attention on the many consequences of obesity.

Knowledge of risks may provide external motivation, which often is not sufficient to induce an individual to enact change toward risk reduction according to Self-Determination Theory (SDT).⁵⁹ As per SDT, which is emerging as a guide for behavioral interventions, if behavior is due to some desire to appease an external demand or attain a reward, it is considered to be regulated by external forces. For those who are not intrinsically motivated to exercise—that is, those who do not find exercise *per se* inherently interesting and satisfying—this external motivation will have to be internalized in order to induce change. Internalization generally will take place for extrinsically motivated activities that an individual deems useful for effective functioning and consistent with one's values and sense of self.⁶⁰



Within SDT, goals can be defined as intrinsic—which generally are focused on self-development and satisfy psychological needs—or extrinsic, which generally do not satisfy psychological needs due to being outwardly focused.^{61,62} Studies have shown that pursuing intrinsic exercise goals, including but not limited to health management, versus extrinsic goals (eg, perceived image, social recognition) is positively associated with self-reported exercise behavior, psychological well-being, and exercise satisfaction.⁶³

Per SDT, an individual will enact adaptive change autonomously once she internalizes the external motivation. Internalization is not an all-or-nothing process. That is, a previously-external motivation can be partially internalized such that the behavior is performed to avoid unpleasant emotions (eg, guilt, anxiety), support conditional self-worth, or enhance ego, but not necessarily to experience pleasure.⁶¹ This type of regulation of behavior is termed “introjected.” If the previously-external motivation is more completely internalized so as to be consistent with one’s values, beliefs, and self-image, it is termed an “identified” regulation.⁵⁹

Both introjected and identified regulations are positively related to self-reported exercise habits among men and women.^{64–66} In a recent study of 1079 men and women who exercise regularly, integrated and identified regulations predicted exercise frequency, while integrated regulation alone predicted exercise duration.⁶⁷ Among women in this study, introjected regulation predicted exercise intensity. In a study of 558 breast cancer survivors, those who met (Australian physical activity) guidelines of 150 minutes per week of moderate or strenuous activity endorsed significantly more identified regulations and intrinsic motivation compared with those who did not meet these guidelines.⁶⁸ Furthermore, 20.2% of physical activity variance was explained by SDT constructs in regression analyses.

Studies incorporating SDT concepts into interventions have demonstrated that these interventions are successful in engendering beneficial lifestyle change. For example, a randomized controlled trial including obese women demonstrated that an intervention emphasizing intrinsic motivation and other forms of exercise self-regulation resulted in significantly greater weight loss and exercise compared with a control group at 1, 2, and 3 years after the 1-year

intervention began.^{69,70} A study including adolescents who participated in an intervention based partly on SDT concepts was successful in inducing decreased consumption of sugary drinks and fast food and increased physical activity.⁷¹ Thus, SDT theory may underscore that motivation for change likely comes from internal rather than external motivations, and external motivators can be internalized depending upon the values of an individual.

In summary, lifestyle change in the form of healthier diet and/or exercise, especially when it results in weight loss, ameliorates many abnormalities of PCOS. Despite well-known benefits of lifestyle change, obesity rates nationwide continue to climb and studies that provide lifestyle change as an intervention experience very large attrition rates. Rather than focus energies on the “how” of weight loss, improving lifestyle change compliance might be better served by focusing on the “why” of adopting healthier behaviors. SDT is one theory that could guide researchers and clinicians in this mission, and future research studies might investigate how SDT concepts are related to behavior in women with PCOS.

Metformin and Other Insulin-Sensitizing Drugs

Metformin and metabolic disorder risk

Metformin and other insulin-sensitizing drugs are well-recognized to improve insulin sensitivity and other metabolic parameters, and therefore often are recommended as treatment alongside lifestyle change in PCOS. In addition to improving metabolic and cardiovascular parameters, much evidence suggests that metformin improves other PCOS clinical outcomes such as menstrual irregularities and live births, endometrial cancer, and hyperandrogenemia and its clinical signs (eg, hirsutism).^{72–79} Other studies, on the other hand, report that metformin has no effect on insulin sensitivity, fasting glucose, lipid profile, or total and free testosterone; these studies, however, included women who were insulin resistant and/or obese and the treatment time was relatively short at 70–90 days.^{80,81}

The above studies are not an exhaustive list of all research to date on the outcomes with regard to metformin treatment among women with PCOS; such a review is beyond the scope of this paper, and has already been achieved by many researchers. Palomba et al⁷⁴



concluded in their comprehensive review that metformin indeed demonstrates effective reduction of many CVD and diabetes parameters in PCOS, but its long-term effect is unknown, and prospective long-term studies are needed. Metformin as first-line treatment remains up for discussion, and the most recent Thessaloniki European Society of Human Reproduction and Embryology-American Society of Reproductive Medicine (ESHRE-ASRM) Sponsored PCOS Consensus Workshop Group consensus on infertility treatment recommends that metformin be prescribed only to women with glucose intolerance.⁸²

Metformin and endometrial cancer risk

It has been estimated that women with PCOS are 3 times more likely to develop endometrial cancer compared with non-PCOS women and up to 35% of women with PCOS have endometrial hyperplasia.^{83,84} Metformin may reduce the likelihood of developing endometrial cancer via several avenues. Metformin helps to regulate ovulation and menstrual cycles,⁸⁵ thereby reducing endometrium exposure to unopposed estrogen stimulation, which is the long-standing proposed mechanism for the increased risk of endometrial cancer in PCOS. Metabolic disorders common in PCOS such as diabetes, hypertension, and obesity also are risk factors for endometrial cancer.^{83,86,87} Recently, a very large prospective study found that the presence of metabolic syndrome and its individual components, particularly elevated fasting glucose levels, predicted endometrial cancer development.⁸⁸ In fact, cancer cells have an increased need for glucose and thrive in hyperglycemic environments.⁸⁹

Researchers have reported that use of metformin results in significant decreases in testosterone and 17- β -estradiol (E_2) levels, both of which may set the stage for endometrial cancer.⁸⁴ Very recently in a case-control study, testosterone and E_2 levels and in vitro invasion of human endometrial adenocarcinoma cells were significantly reduced after 6 months of treatment with 850 mg metformin twice per day.⁷⁹ Similar results have been reported by other researchers as well.⁹⁰ Metformin may also exert anti-inflammatory effects in the endometrium by reducing vascular endothelial growth factor (VEGF),⁹¹ which has been established as playing a role in the development and exacerbation of endometrial cancer.⁹² The role of inflammation and

anti-inflammatory drugs in PCOS will be discussed later in this paper.

Metformin may directly affect the hyperandrogenemic environment in the endometrium as well. Testosterone appears to induce insulin resistance in the endometrium, leading to abnormal glucose metabolism and abnormal endometrial function,^{93,94} and metformin might improve this abnormal environment. For example, Zhang and Liao⁹³ examined ex vivo cultured endometrial glandular epithelial cells from normal-weight women between ages 32 and 45 with normal menstrual cycles to observe how high androgen levels and metformin influenced glucose metabolism. A PCOS-like environment was created in the endometrium by stimulation with androgens. Adding metformin to this environment resulted in significant upregulation of insulin receptor substrate-1 (IRS-1), which indicated that metformin improved insulin resistance in the endometrium. These results suggest that the relatively low expression in the endometrium of (IRS-1) that appears to be due to elevated androgen levels can be reversed by metformin.

Metformin and pregnancy

Metformin appears to restore menstrual cycles and also improve fertility in initially anovulatory and oligo-ovulatory women with PCOS.^{95–99} Studies have demonstrated that metformin affects the endometrium so as to create an environment more suitable for pregnancy. For example, case-control studies have shown that metformin improves endometrial vascular function and penetration, arterial blood flow, and glycodelin concentration, which is a marker of endometrial function that is relatively low in women who miscarry.^{95,100}

CC is an established ovulation induction agent, and recent research has focused on comparing CC to metformin rather than on the effects of CC per se. Whether metformin is better than CC with regard to birth rate has been an ongoing debate and the topic of numerous research studies. Because CC has proven more effective in inducing ovulation than metformin but appears to exert disadvantageous effects on the endometrium and cervical mucus, creating an environment less likely to result in pregnancy,¹⁰¹ studies investigating CC versus metformin have begun considering live birth rate as the most appropriate outcome.



Even meta-analyses, however, arrive at differing conclusions. Recently, a Cochrane review established that metformin is not necessarily more effective than CC with regard to ovulation and pregnancy rates.¹⁰² A very recent decision-analytic study determined that combining metformin and CC was most effective in achieving live birth among women with PCOS compared with either metformin or CC alone.¹⁰³ A comprehensive review of the effects of metformin in PCOS concluded that combination treatment is no better with regard to birth rate than either metformin or CC alone; the choice of one option or the other should be determined with the patient's wishes in mind given that CC generally induces ovulation sooner than metformin but also comes with an increased risk of multiparity.⁷⁴

Some studies suggest that a factor to consider in the CC versus metformin debate may be obesity. The most recent meta-analysis that could be found on this topic concluded that metformin and CC are similarly effective in inducing ovulation and improving pregnancy and live birth rates among PCOS women with a BMI ≤ 32 .¹⁰⁴ An empirical study by these researchers revealed that, not surprisingly, within a group of PCOS women on metformin of BMI > 32 , BMI impacted pregnancy rates such that women with a relatively lower BMI were more likely to achieve pregnancy.¹⁰⁵ Furthermore, BMI had a greater impact on pregnancy rate in the metformin group than it did in the placebo group. BMI had a marginally significant ($P = 0.062$) impact on pregnancy rate for women with BMI ≤ 32 when comparing the pregnancy rate in the combination (metformin+CC) group versus CC alone. Interestingly, fasting insulin did not impact pregnancy rates among obese or non-obese women receiving metformin, CC, or both, suggesting that the impact of obesity on pregnancy may not be acting via insulin action. These researchers previously reported that there was no difference in pregnancy or live birth rates among groups of PCOS women with BMI ≤ 32 prescribed metformin, CC, or both; nor among PCOS women with BMI > 32 treated with either placebo or metformin, but all study drugs were stopped once pregnancy was achieved.¹⁰⁶

Other insulin-sensitizing drugs such as rosiglitazone and pioglitazone may be effective in reducing insulin resistance and thus improving the metabolic and menstrual cycle characteristics among women

with PCOS. Fetal safety, however, has not been established and it is recommended that they be discontinued once pregnancy has occurred. Metformin generally is recommended first before a trial of these drugs.¹⁰²

In summary, metformin appears to improve insulin sensitivity and perhaps other abnormal metabolic and pro-inflammatory parameters, thereby decreasing the likelihood of developing metabolic syndrome, diabetes, and cardiovascular disease. Due to these and its apparent anti-androgenic effects, metformin also may aid in increasing pregnancy and birth rates and also reduce risk of endometrial cancer. Whether metformin is preferred over CC for fertility treatment is still under debate, and factors potentially affecting the success of one treatment over the other (eg, obesity) remain elusive.

Other Drugs and Medical Procedures for Infertility Surgery

Bilateral laparoscopic ovarian surgery is another option for women with PCOS who are resistant to CC, and it appears to be as effective with regard to pregnancy rates as gonadotropin treatment without side effects of multiple pregnancies or ovarian hyper stimulation syndrome.¹⁰⁷

Aromatase inhibitors

A recent meta-analysis comparing the effectiveness of letrozole versus CC found that both were equally effective with regard to pregnancy, abortion, and multiple pregnancy rates.¹⁰⁸ Letrozole may be more effective than laparoscopic ovarian drilling in CC-resistant PCOS women with regard to ovulation rate and endometrial thickness.¹⁰⁹ Another aromatase inhibitor, anastrozole, has been shown to be as effective as CC with regard to ovulation, pregnancy, and miscarriage rates, and it induced a significantly thicker endometrium.¹¹⁰ A thicker endometrium has been shown to improve pregnancy outcome in women undergoing intrauterine insemination.¹¹¹ Despite some concerns about a teratogenic effect, a couple of studies in humans have provided evidence that aromatase inhibitors are not teratogenic.^{112,113} Thus, aromatase inhibitors may be an alternative treatment for ovulation induction and pregnancy among women with PCOS, but more trials are needed to establish its efficacy.¹¹⁴



Gonadotropins

Exogenous gonadotropin therapy can induce pregnancy in CC-resistant women. Gonadotropins do not exert an antiestrogenic effect on the endometrium as does CC, but can induce multiple follicle development and therefore ovarian hyper stimulation syndrome and risk of multiple pregnancy. Thus, its use should be limited to PCOS women who do not respond to another type of treatment.²⁷

Anti-Inflammatory Drugs

That women with PCOS have higher levels of pro-inflammatory cytokines [eg, tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6)] compared with controls is supported by a great deal of research.^{25,115,116} Inflammation is related to both cardiovascular disease and diabetes, and more recently, evidence shows that increased inflammation also is related to cancer.^{117–120} There is some evidence that a pro-inflammatory environment may exist in the uterus due to amenorrhea/oligomenorrhea and unopposed estrogen stimulation of the endometrium.¹¹⁸ In fact, knockout mice that lack a progesterone receptor exhibit uterine hyperplasia and inflammation.¹²¹

Several studies have found that the risk of several cancers is reduced among those who report long-term use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), also supporting a link between inflammation and cancer risk.^{122–126} With regard to endometrial cancer, several studies have found no relationship between self-reported aspirin or other NSAID use and endometrial cancer.^{127–130} Other studies have demonstrated that use of aspirin or other NSAIDs may decrease the risk of endometrial cancer,¹³¹ especially among women who are obese.^{132,133} In their review, Modugno et al¹¹⁸ describe several possible pathways through which NSAIDs might prevent endometrial cancer, including via mechanisms reducing COX-2, inhibiting aromatase, improving insulin signaling, trapping reactive oxygen species, reoxygenating injured tissues, and reducing TNF- α expression.

Anti-inflammatory drugs may also impact pregnancy. A case-control study assessed the effect of 100 mg aspirin daily among 298 women undergoing ovarian hyper stimulation prior to IVF, who started the aspirin on the 21st day of their preceding menstrual cycle and continued through early pregnancy. Those in the

aspirin group exhibited significantly higher number of retrieved follicles and oocytes, serum E₂ levels, uterine and ovarian pulsatility indices, and pregnancy and implantation rates.¹³⁴

Although treatment with aspirin or other anti-inflammatories is not standard practice for treating PCOS, emerging research recognizes the pro-inflammatory state often inherent in PCOS and also the potentially beneficial effects of anti-inflammatory drugs. Although research on this topic is neither sufficient nor conclusive to recommend such drugs for standard treatment, it broadens the scope of potential treatment options for PCOS in the future.

Statins

The metabolic syndrome is quite common among women with PCOS with prevalence rates of 43%–46%,^{135,136} which is not surprising given that PCOS often is characterized by insulin resistance and obesity. Additionally, it appears that all non-HDL cholesterol is higher among women with PCOS compared with controls matched for BMI in a recent meta-analysis,¹³⁷ which provides evidence for dyslipidemia in women with PCOS as well.

Statins can improve lipid profile in PCOS and also many other aspects of PCOS such as total and free testosterone, hirsutism score, insulin resistance (measured by HOMA-IR), and C-reactive protein^{138,139} and also diastolic blood pressure.¹⁴⁰ Although some meta-analyses have concluded that statins may slightly increase the risk for type 2 diabetes in the general population,^{141,142} if lifestyle changes fail to improve one's lipid profile and other criteria of metabolic syndrome, statins may be beneficial in women with PCOS.¹³⁷

The Oral Contraceptive (OC) Pill

For women with PCOS who do not wish to become pregnant, the combined oral contraceptive (OC) generally is first-line treatment, especially to reduce hirsutism and acne.^{143–145} Although all OCs will suppress ovulation, thereby inhibiting production of androgens in the ovary and reducing serum androgen levels, some OCs are more effective than others in treating clinical signs of hyperandrogenism, depending upon the androgenic properties of the progestin.

Several newer OCs contain less androgenic progestins, such as norethindrone, desogestrel, and



norgestimate, while other progestins (ie, norgestrel, levonorgestrel) exert relatively strong androgenic effects.¹⁴⁶ One strong progestin, cyproterone acetate, acts as an androgen receptor antagonist and effectively reduces hirsutism and acne,^{144,147,148} but it is not available in the United States. Another potent progestin, drospirenone, is derived from spironolactone and, since it is both antiandrogenic and antimineralocorticoid, improves acne, hirsutism, and edema (which is caused by use of some OCs) after an average of 6–9 months of treatment.¹⁴⁹ However, drospirenone is contraindicated among those with predisposed to hyperkalemia.

OCs can cause side effects that render them absolutely contraindicated for those who are pregnant, use tobacco (especially if older than 35), or have a history of thromboembolic, heart, or liver disease. Relative contraindications for OC use include current breastfeeding, current malignancies, and history of migraines and hypertension.¹⁵⁰

Few recent studies have compared how different progestins in OCs affect several clinical and metabolic parameters in PCOS. Drospirenone- (eg, YAZ) and desogestrel- (eg, Mircette) containing pills have been compared on clinical, endocrine, and metabolic indices in Indian women with PCOS.¹⁵¹ Before treatment, only 2 patients in the drospirenone group and 1 patient in the desogestrel group had regular menstrual cycles out of 30 patients in each group. Cycles become regular in all patients in both groups, but significantly more patients in the drospirenone group (44.8% versus 17.2%) continued to have regular cycles for 6 months after stopping treatment. Hirsutism, but not acne, also decreased significantly in the drospirenone group after treatment. Drospirenone also appeared to help with weight loss, as this group lost a significant amount of weight at the end of 6 months of treatment, while the women in the desogestrel group on average gained weight. Drospirenone demonstrated improvements on several metabolic parameters including LDL cholesterol, HDL cholesterol, blood pressure, and insulin sensitivity compared with desogestrel. Triglycerides rose significantly in both groups, however. Studies on the effects of another recently-developed progestin, chlormadinone acetate (which is not available in the United States), have demonstrated that it reduces fat mass,¹⁵² improves lipids,¹⁵³ and reduces acne and hirsutism,¹⁵⁴ but has no effect on insulin sensitivity.^{153,154}

OCs and endometrial cancer prevention

Based on studies over the past 50+ years, it is thought but not conclusively proven that exposure to unopposed estrogen, common in PCOS due to amenorrhea/oligomenorrhea, induces endometrial hyperplasia and therefore is a risk factor for endometrial cancer. Studies have suggested that length of time (measured by number of years of menstruation and parity) of exposure to estrogen^{155,156} and estrogen replacement therapy are associated with a higher risk of endometrial cancer^{157,158} but adding progestins to the therapy significantly decreased that risk.¹⁵⁹ Thus, one can conclude—as many researchers and clinicians have—that chronic anovulation, and therefore PCOS, is associated with an increased risk of endometrial hyperplasia and carcinoma.¹⁶⁰

Since OCs induce regular menstrual cycles and therefore help to limit endometrial exposure to unopposed estrogen, OCs generally are considered to be first-line treatment for prevention of endometrial cancer despite lack of long-term studies demonstrating that OC prevents cancer. A recent Cochrane review, in fact, asserted that current studies are insufficient from which to draw conclusions about the effectiveness of the OC in reducing risk for endometrial cancer.⁷⁶

It is difficult to determine to what extent the different abnormalities that are common in PCOS contribute to endometrial cancer risk, as diabetes, hypertension, hyperandrogenemia, and obesity individually also are risk factors for endometrial cancer in addition to amenorrhea/oligomenorrhea. Thus, because PCOS often is characterized by several endometrial cancer risk factors, reducing this risk might best be accomplished by a treatment approach incorporating commonly-prescribed anti-androgen therapy and lifestyle changes toward improved metabolic parameters.

Thus, OC inhibits androgen production and therefore generally improves hyperandrogenemic signs, including acne, hirsutism, and alopecia, and usually is the preferred treatment for women who do not wish to become pregnant. OC also may decrease risk of endometrial cancer, although long-term studies do not exist to confirm this hypothesis. Some newer androgens, such as drospirenone, may also improve other indices such as metabolic and lipid parameters and weight gain, but more studies are needed to duplicate these findings.



Other Drugs to Treat Hirsutism and Acne

Antiandrogens

In addition to or instead of OC, several antiandrogens can be prescribed to women with PCOS who wish to reduce hyperandrogenic clinical signs (eg, hirsutism, acne, alopecia) of PCOS. Spironolactone, an aldosterone antagonist, has been shown to improve hirsutism and acne^{144,161} and is most effective when combined with an OC.¹⁶² It is contraindicated in pregnancy and for women who have an increased risk of breast cancer, and it also can cause hyperkalemia at high doses or in women with cardiac or renal compromise.¹⁴⁴ Flutamide is a nonsteroidal selective antiandrogen that is as effective in treating hirsutism as is spironolactone, and in combination with metformin is more effective in improving adiposity, inflammatory, and lipid profile parameters than is OC treatment,¹⁶³ but its use is limited by hepatic toxicity and financial expense.¹⁴⁴ Finasteride, which inhibits production of dihydrotestosterone, is effective in reducing hirsutism, but generally is less effective with regard to improving hirsutism when compared with spironolactone or flutamide.¹⁶⁴ Finasteride does not appear to be as effective in reducing acne as is flutamide.¹⁶⁵ All antiandrogens should be avoided during pregnancy due to possibility of feminizing a male fetus.

Glucocorticoids

Glucocorticoids (eg, prednisone, dexamethasone) suppress adrenal androgen secretion and have been added to CC in CC-resistant PCOS women to improve ovulation and pregnancy rates and also inhibit an adverse antiestrogenic effect on the endometrium.^{166,167} Glucocorticoids also have been considered as treatment for clinical manifestations of hyperandrogenism among women with PCOS. Glucocorticoid use should be considered after trials of other medications and only if adrenal androgen level is excessive, however, due to glucocorticoid-associated worsening of insulin resistance¹⁶⁸ and its association with osteoporosis.²⁷

Gonadotropin-releasing hormone agonist (GnRHa)

Among those who are not responsive to OC, gonadotropin-releasing hormone agonist (GnRHa) is another

treatment option for acne and hirsutism. It has been demonstrated to be more effective when combined with OC than OC alone in reducing hirsutism score.^{169,170} In another study including hirsute women with PCOS, GnRHa alone and also in combination either OC or flutamide each comparably reduced hirsutism.¹⁷¹ GnRHa has been shown to improve acne as well¹⁷² but very little research has compared GnRHa to other drugs with regard to acne improvements. GnRH-a treatment is expensive, however, and can cause menopausal symptoms, headaches, and bone loss.^{144,173}

Summary

There are several medical treatment options for the numerous diverse abnormalities common in PCOS, with some of those options (eg, metformin, OC) capable of ameliorating more than one abnormality. OC and CC are established drugs to treat PCOS, and metformin, with its metabolic effects, has emerged as another typical medication prescribed to women with PCOS. Aromatase inhibitors, statins, and anti-inflammatory drugs show some promise as potential treatment options, but much more research is needed in order to demonstrate efficacy and benefit over cost. Weight loss and/or increased physical exercise both result in improvements in many PCOS parameters, but compliance with lifestyle change, even in clinical trials, is disappointing. Evaluating barriers—logistical and psychological—to lifestyle change may be important topics to address during a clinical appointment with a woman with PCOS.

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