

Treatment options for polycystic ovary syndrome

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Abstract: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women. The clinical manifestation of PCOS varies from a mild menstrual disorder to severe disturbance of reproductive and metabolic functions. Management of women with PCOS depends on the symptoms. These could be ovulatory dysfunction-related infertility, menstrual disorders, or androgen-related symptoms. Weight loss improves the endocrine profile and increases the likelihood of ovulation and pregnancy. Normalization of menstrual cycles and ovulation could occur with modest weight loss as little as 5% of the initial weight. The treatment of obesity includes modifications in lifestyle (diet and exercise) and medical and surgical treatment. In PCOS, anovulation relates to low follicle-stimulating hormone concentrations and the arrest of antral follicle growth in the final stages of maturation. This can be treated with medications such as clomiphene citrate, tamoxifen, aromatase inhibitors, metformin, glucocorticoids, or gonadotropins or surgically by laparoscopic ovarian drilling. In vitro fertilization will remain the last option to achieve pregnancy when others fail. Chronic anovulation over a long period of time is also associated with an increased risk of endometrial hyperplasia and carcinoma, which should be seriously investigated and treated. There are androgenic symptoms that will vary from patient to patient, such as hirsutism, acne, and/or alopecia. These are troublesome presentations to the patients and require adequate treatment. Alternative medicine has been emerging as one of the commonly practiced medicines for different health problems, including PCOS. This review underlines the contribution to the treatment of different symptoms.

Keywords: treatment, polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women. Its prevalence among infertile women is 15%–20%. The etiology of PCOS remains unclear; however, several studies have suggested that PCOS is an X-linked dominant condition. Women with PCOS have abnormalities in the metabolism of androgens and estrogen and in the control of androgen production. High serum concentrations of androgenic hormones, such as testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEAS), may be encountered in these patients. However, individual variation is considerable, and a particular patient might have normal androgen levels. PCOS is also associated with peripheral insulin resistance and hyperinsulinemia, and obesity amplifies the degree of both abnormalities. Insulin resistance in PCOS can be secondary to a postbinding defect in insulin receptor signaling pathways, and elevated insulin levels may have gonadotropin-augmenting effects on ovarian function. In addition, insulin resistance in PCOS has been associated

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with adiponectin, a hormone secreted by adipocytes that regulates lipid metabolism and glucose levels. Both lean and obese women with PCOS have lower adiponectin levels than women without PCOS. A proposed mechanism for anovulation and elevated androgen levels suggests that under the increased stimulatory effect of luteinizing hormone (LH) secreted by the anterior pituitary, stimulation of the ovarian theca cells is increased. In turn, these cells increase the production of androgens (eg, testosterone, androstenedione). Because of a decreased level of follicle-stimulating hormone (FSH) relative to LH, the ovarian granulosa cells cannot aromatize the androgens to estrogens, which leads to decreased estrogen levels and consequent anovulation. Growth hormone and insulin-like growth factor 1 may also augment the effect on ovarian function.^{1,2}

In this review, the state of the art in the treatment of different aspects of PCOS, from anovulation to hyperandrogenism, is discussed, with a particular emphasis on the emerging new modalities of treatment such as alternative therapy.

Diagnosis of PCOS

The clinical manifestation of PCOS varies from a mild menstrual disorder to severe disturbance of reproductive and metabolic functions. Women with PCOS are predisposed to type 2 diabetes or develop cardiovascular disease.³ Factors implicated in the low fertility in these patients include anovulation, increased risk of early miscarriage, and late obstetric complications. Clinical manifestations include menstrual disorders and signs of hyperandrogenism. Although not universal and not part of the definition, insulin resistance and obesity are also extremely common accompaniments of this syndrome.⁴ This phenotypic nonuniformity and the variability of presentation have made it difficult to define the syndrome.

The 1990 National Institutes of Health (NIH)-sponsored conference for definition required oligo-ovulation, clinical or biochemical hyperandrogenism, and the exclusion of other known disorders, such as late-onset congenital adrenal hyperplasia and Cushing's syndrome⁵ (Table 1). The diagnostic criteria of the syndrome were revised by the Rotterdam European Society for Human Reproduction/American Society of Reproductive Medicine (ASRM)-sponsored PCOS consensus workshop group in 2003, where the following criteria were established: oligo/amenorrhea, clinical and biochemical signs of hyperandrogenism, and sonographically confirmed PCOS.⁶ Two of the three criteria are required for diagnosis (after exclusion of other etiologies such as congenital adrenal hyperplasia, androgen-secreting tumors, or Cushing's syndrome). Sonographic features of PCOS

Table 1 Diagnostic criteria

Organization/group	Year	Criteria
National Institutes of Health	1990	Both hyperandrogenism and chronic anovulation ⁵
Rotterdam European Society for Human Reproduction/American Society of Reproductive Medicine-sponsored PCOS consensus workshop group	2003	Two of the following conditions: hyperandrogenism, chronic anovulation, polycystic ovary ⁶
Androgen Excess Society	2006	Hyperandrogenism and ovarian dysfunction (including infrequent or irregular ovulation or anovulation) and/or polycystic ovary ⁷

Abbreviation: PCOS, polycystic ovary syndrome.

include the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter and/or increased ovarian volume (>10 mL). This is regardless of follicle distribution or ovarian stromal echogenicity. One ovary fulfilling this definition is sufficient to define PCOS.^{2,7} It is recognized that some women with sonographic findings of PCOS may have regular cycles without clinical or biochemical signs of hyperandrogenism. Although this has been a practical working definition, others believe that hyperandrogenism should be an integral part of the definition.

Ovulatory women with PCOS seem to be less insulin resistant than anovulatory women with PCOS;⁸ further, a study published in 2007 suggests that women with PCOS,⁹ chronic anovulation, and normal androgen levels are not insulin resistant. These observations limit the usefulness of the Rotterdam criteria, and accordingly an expert panel of the Androgen Excess Society (AES) recommended that PCOS should be considered a disorder of androgen excess and that the NIH diagnostic criteria should be used.⁷ The AES also recommended that women with hyperandrogenism, PCOS, and ovulatory cycles should be considered to have a PCOS phenotype; thus, hyperandrogenism and infrequent or irregular ovulation, as well as hyperandrogenism, regular ovulation, and PCOS, fulfill AES criteria for PCOS.

Management of PCOS

Management of women with PCOS depends on the symptoms. These could be ovulatory dysfunction-related infertility, menstrual disorders, or androgen-related symptoms.

Weight reduction

There is some evidence that PCOS-related hyperandrogenism causes central obesity with a high waist/hip ratio independent

of the body mass index (BMI). It is well established that obesity is associated with anovulation, miscarriage, or late pregnancy complications (such as pre-eclampsia and gestational diabetes).^{10,11} Obesity is observed in 35%–60% of women with PCOS and is related to lack of or delayed response to different treatments such as clomiphene citrate (CC), gonadotropins, and surgical treatment of diathermy via laparoscopy.¹²

Weight loss improves the endocrine profile and increases the likelihood of ovulation and pregnancy. Normalization of the menstrual cycles and ovulation could occur with modest weight loss as little as 5% of the initial weight.¹³ Weight loss can improve not only circulating androgen and glucose levels but also ovulation and pregnancy rates in obese women with PCOS; however, weight loss is only recommended for those who are overweight with a BMI > 25–27 kg/m². The treatment of obesity includes modifications in lifestyle (diet and exercise) and medical and surgical treatment. All these treatments must be performed during the preconception period and not jointly with reproduction therapies.

Diet

Diets recommended for obese PCOS patients are low in calories with a reduced carbohydrate intake, and any form of these diets can produce the 5%–10% loss necessary to re-establish ovarian function in these patients. In 2005, Reaven suggested that low-fat diets produce a decrease in hyperinsulinemia, which improves metabolic effects.¹⁴

Exercise

Several studies have attempted to establish the role of exercise in the treatment of obese PCOS patients.¹⁵ None found significant differences when different diets, associated or not with exercise, were compared, although a longer weight loss maintenance time did appear to be associated in these patients. An increase in physical activity is recommended for PCOS patients, although this often presents limitations.¹⁶ A knowledge gap exists regarding the optimal type, duration, and frequency of exercise.

Bariatric surgery

Recently, bariatric surgery has been advocated as a strategy for weight loss in the morbidly obese. In addition, if spontaneous weight loss cannot be achieved with diet and exercise, bariatric surgery can be offered. Two primary approaches, restrictive and combined restrictive, and malabsorptive procedures, adjustable gastric banding, and the Roux-en-Y gastric bypass, are commonly performed. Not surprisingly,

in 17 women with PCOS and a mean BMI of 50.7 kg/m², bariatric surgery resulted in an average loss of 41 ± 9 kg in 12 months and improvements in ovulation, insulin resistance, hyperandrogenism, and hirsutism.¹⁷ In a group of 12 PCOS patients available for follow-up after bariatric surgery for morbid obesity, regular cycles were restored in all.¹⁷ Of note, women who have had bariatric surgery are at increased risk for nutritional deficiencies, including protein, iron, vitamin B₁₂, folate, vitamin D, and calcium; however, no consensus exists regarding optimal nutritional screening and supplementation.

Ovulation induction

In PCOS, anovulation relates to low FSH concentrations and the arrest of antral follicle growth in the final stages of maturation. Excess LH, androgens, and insulin may individually or collectively play a direct or indirect role in this process, augmenting steroidogenesis but arresting follicular growth. For many women, anovulatory infertility is the presenting complaint. Medications and other options available for the induction of ovulation are reviewed in the following sections.

CC

CC constitutes one of the first-line treatments for ovulation induction in these patients, as it is economical, is straightforward, has few adverse effects, and requires little monitoring.¹⁸ CC is an estrogen receptor antagonist that interferes with negative feedback of the estrogen-signaling pathway, resulting in increased availability of FSH. Increased FSH leads to follicular growth, followed by an LH surge and ovulation. CC is indicated in patients with PCOS and anovulation with normal FSH levels, but it has certain limitations in patients with a BMI > 30 and advanced age. Legro et al found significant differences in pregnancy rates in patients with a BMI > 30 compared with those with a BMI < 30.¹⁹

Doses of 50–150 mg are administered for 5 days, starting on days 3 or 5 of a progestin-induced or spontaneous cycle. CC produces ovulation in 75%–80% of PCOS patients, although when the gestation rate is assessed, it nears 22% per ovulation cycle.²⁰ These differences in results are attributed to the antiestrogenic effects of CC, mainly on the endometrium and the cervical mucus.¹⁸ The live birth rate following 6 months of clomiphene ranged from 20% to 40%. Furthermore, the majority of pregnancies occurred within the first six ovulatory cycles following the initiation of treatment.¹⁹ Multiple pregnancy rates are under 10%, and hyperstimulation syndrome is rare. Tamoxifen is another

oral ovulatory agent that is similar to CC in its mechanism of action, but it lacks its antiestrogenic effect on the cervix and endometrium. It can be used as an alternative to CC in case of CC resistance or failure.

Metformin

Metformin is a biguanide currently used as an oral antihyperglycemic agent and is approved by the US Food and Drug Administration (FDA) to manage type 2 diabetes mellitus. The use of metformin is associated with increased menstrual cyclicity, improved ovulation, and a reduction in circulating androgen levels.²¹ Metabolic benefits are enhanced in the presence of weight loss, and weight loss itself may be enhanced in the presence of metformin. Its primary clinical action is to inhibit hepatic glucose production, although it also decreases intestinal glucose uptake and increases insulin sensitivity in peripheral tissues.²² Metformin likely plays its role in improving ovulation induction in women with PCOS through a variety of actions, including reducing insulin levels and altering the effect of insulin on ovarian androgen biosynthesis, theca cell proliferation, and endometrial growth. In addition, potentially through a direct effect, it inhibits ovarian gluconeogenesis and thus reduces ovarian androgen production.

Several dose regimens have been proposed.²³ In order to increase patient tolerance, metformin is started at 500 mg daily with food. After 1 week, the dose is increased to 1000 mg for another week and then to 1500 mg daily. The target dose is 1500–2550 mg/day (500 or 850 mg three times daily). Clinical response is usually seen at the dose of 1000 mg daily. It appears that some PCOS patients who do not respond to metformin at a dose of 1500 mg daily will respond favorably to 2000 mg daily. The most common side effects of metformin are nausea and diarrhea. Lactic acidosis has been described mainly in patients with renal impairment, congestive heart failure, and sepsis. Traditionally, oral hypoglycemic agents have been regarded as teratogenic, and their use is contraindicated in pregnancy. However, an increasing amount of data supports their safety when used throughout the pregnancy. Glueck et al reported no major birth defects and no effect on motor or social development of infants at 3 and 6 months of age.²⁴ Compared with the control group of women who did not receive metformin, the incidence of gestational diabetes in the treated group was significantly lower.

To define the exact role of metformin in ovulation induction, it is crucial to distinguish two different indications. In naive PCOS, metformin, as compared with placebo, has been shown to improve ovulation rates, but metformin did not exert

significant advantage over CC with respect to cumulative ovulation, pregnancy, or live birth rates.²⁵ The combined approach of metformin plus CC is not better than CC or metformin monotherapy in naive PCOS.²⁶ In CC-resistant patients, metformin has no benefit over placebo in ovulation, pregnancy, and live birth rates as a single agent, but the combination of metformin and CC significantly improved ovulation and pregnancy rates when compared with CC alone. However, combined therapy did not improve the odds of live birth.²⁷ Metformin pretreatment improves the efficacy of CC in PCOS patients with CC resistance.²⁸

Troglitazone is another insulin-sensitizing drug that has been shown to improve ovulation and increase pregnancy rates. However, due to its hepatotoxic effect, it has been withdrawn from the market.²⁹ Another drug in the same category, rosiglitazone (8 mg/day), has been shown to enhance both spontaneous and clomiphene-induced ovulation in women with PCOS with a mean BMI of 35.5–38.5 kg/m². Pioglitazone appears to be effective as well; however, the study is still limited. Although both rosiglitazone and pioglitazone have little short-term risk, fetal safety has not been established (pregnancy category C of the US FDA guidelines). If used, they should be discontinued as soon as pregnancy has been established. Recently, Tang et al updated the Cochrane review about insulin-sensitizing drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with PCOS, oligo/amenorrhea, and subfertility and concluded that metformin is still of benefit in improving clinical pregnancy and ovulation rates. However, there is no evidence that metformin improves live birth rates whether it is used alone or in combination with clomiphene, or when compared with clomiphene. Therefore, the use of metformin in improving reproductive outcomes in women with PCOS appears to be limited.³⁰

Aromatase inhibitors

Selective aromatase inhibitors such as anastrozole and letrozole are promising new ovulation-inducing agents. They are reversible and highly potent. Unlike CC, which has a half-life of 5–7 days, the mean half-life of anastrozole and letrozole is ~45 h only. To date, letrozole has been studied much more extensively than anastrozole.³¹ Letrozole was introduced as an assisted reproduction treatment following the appearance of multiple adverse effects of CC, CC's scant therapeutic success, and the complexity of gonadotropin treatment. Letrozole inhibits estrogen production in the hypothalamus–pituitary axis, which implies an increase in gonadotropin-releasing hormone (GnRH) and FSH. It is

believed that there exists a relative decrease in aromatase in women with PCOS, which reduces the production of follicles responsible for efficacious ovulation. To use this relative deficit, aromatase inhibitors were considered in order to provoke ovulation, because their selective action of blocking the peripheral passage of androgens to estrogens reduces the quantity of estrogens, thereby producing positive feedback in the pituitary, increasing FSH, and optimizing ovulation. The advantage of letrozole is that it avoids peripheral antiestrogenic effects on the endometrium while stimulating monofollicular growth.³² Letrozole at 2.5–5 mg is administered for 5 days and may be accompanied by FSH (at the normal doses for PCOS patients) and human chorionic gonadotropin (hCG; 10,000 IU) when the follicle diameter reaches 18 mm in order to program the ovulation. However, in a prospective randomized trial comparing letrozole with clomiphene, pregnancy rates were similar. Although Novartis Pharmaceuticals (Basel, Switzerland) has warned against the use of letrozole for ovulation induction (owing to possible teratogenicity), a comparison with clomiphene did not demonstrate increased rates of major or minor malformations.³³

Glucocorticoids

Glucocorticoids such as prednisone and dexamethasone have been used to induce ovulation. Elnashar et al demonstrated that induction of ovulation by adding dexamethasone (high dose, short course) to CC in CC-resistant PCOS with normal DHEAS is associated with no adverse antiestrogenic effect on the endometrium and higher ovulation and pregnancy rates in a significant number of patients.³⁴

In PCOS patients with high adrenal androgen, low-dose dexamethasone (0.25–0.5 mg) at bedtime can be used.³⁵ In a study of 230 women with PCOS who failed to ovulate with 200 mg of CC for 5 days, addition of 2 mg of dexamethasone from days 5–14 is associated with a higher ovulation rate and cumulative pregnancy rate.³⁶ Enthusiasm for their use is dampened, however, by their potential adverse effects on insulin sensitivity; therefore, prolonged use should be discouraged.

Gonadotropins

The second possible line of therapy after resistance to CC has been demonstrated in women with PCOS is exogenous gonadotropins.³⁷ The mechanism of action of gonadotropins is to induce ovulation, maintain and provoke optimum follicle growth via the controlled administration of FSH, and achieve a follicle capable of being fertilized. Unlike CC, gonadotropin does not exert a peripheral antiestrogenic effect. The main

drawback of gonadotropins is that they provoke multiple follicle development, thereby increasing the risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. Treatment with FSH is expensive, is time consuming, and requires expertise and stringent monitoring. OHSS is related to hCG-mediated production of vasoactive mediators after gonadotropin-induced multifollicular development.³⁸

Several treatment protocols have been advocated, such as step-up, low-dose step-up, and step-down regimens. The ASRM recommends low-dose gonadotropin protocols.³⁹ A step-up dose-finding approach favoring unifollicular development is recommended. The step-up regimen starts with a minimum dose (37.5–50 IU/day), which increases according to the lack of follicle response. Control is made by ultrasound, and the regimen is modified after 1 week of no follicle growth with a 50% increase each time as required. HCG is used as a surrogate for the LH surge, leading to maturation of the oocyte, rupture of the follicle, and formation of the corpus luteum. The step-down regimen starts with the maximum recommended dose, which is reduced as a follicle response is achieved. The dose is reduced by 50% each time the regimen is changed. Recent studies have demonstrated greater safety for patients using the step-up regimen.⁴⁰

In 2006, the ASRM advocated caution and strict control when blood estradiol levels exceed 2500 pg/mL during induction.³⁹ Current recommendations suggest withholding hCG administration in the presence of more than two follicles >16 mm or more than one follicle >16 mm and two additional follicles >14 mm, or if serum estradiol levels are between 1000 and 2500 pg/mL, particularly in women <38 years old without any other infertility factors. Overall, low-dose regimens resulted in a monofollicular ovulation rate of ~70%, a pregnancy rate of 20% per cycle, and a multiple live birth rate of 5.7% while maintaining a low incidence of multiple pregnancies (<6%) and OHSS (<1%).⁴¹ A maximum of six cycles with gonadotropins is recommended because no response with six cycles signifies resistance.

Laparoscopic ovarian diathermy

In clomiphene-resistant PCOS women who are unable to comply with the close monitoring necessary for gonadotropin administration, bilateral laparoscopic ovarian surgery with monopolar electrocautery (multiple controlled perforation of the ovary) or laser is an acceptable alternative; both modalities confer similar results.⁴² Laparoscopic ovarian diathermy (LOD) is associated with lower multiple gestation rates than gonadotropins. In a Cochrane Database Systematic Review article, there was no evidence of a

difference in live birth rate and miscarriage rate in women with clomiphene-resistant PCOS undergoing LOD versus gonadotropin treatment. It appears to be more effective in patients with high LH, and significant reductions in LH and androgens have been shown following surgery. LOD restores menstrual regularity in 63%–85% of women, and the beneficial effects on reproductive outcomes seem to last for several years in many women.⁴³ Treatment with metformin is equally efficacious in correcting the clinical, endocrine, and metabolic abnormalities associated with PCOS.⁴⁴

In vitro fertilization techniques

The last possibility for achieving a full-term pregnancy in women with PCOS is to use in vitro fertilization (IVF) techniques.⁶ Patients with PCOS are characterized by anovulatory cycles that conceptually are not an indication for IVF techniques. These techniques are used as a last resort when treatments with CC, gonadotropins, and letrozole have failed. IVF is the first choice in cases of concomitant diseases both in women (severe endometriosis, tubal obstruction, etc) and men (azoospermia, male factor) that reduce the effectiveness of other techniques. Because of the increased risk of multiple gestations (up to 10%) with gonadotropin induction in anovulatory women with PCOS, IVF is a reasonable alternative for women seeking pregnancy. IVF with a single embryo transfer significantly reduced the risk of multiple gestation.⁴⁵ IVF allows the placement of only one embryo or for cryopreservation of all embryos, with transfer of a single embryo in a subsequent cycle with endometrial but not ovarian stimulation IVF.

Several stimulation protocols have been published for the treatment of patients with PCOS undergoing IVF, including combinations or isolated use of clomiphene, human menopausal gonadotropins, recombinant FSH, GnRH agonists, and GnRH antagonists.^{46,47} According to the 2008 ASRM consensus conference, the most commonly employed protocol is a long FSH desensitization protocol in which an agonist is started in the early, mid-, or late luteal phase in the preceding cycle or in the follicular phase until hCG administration. Stimulation with gonadotropins is started when pituitary and ovarian suppression has been achieved.⁴⁸ A meta-analysis published in 2006, which studied the results of conventional IVF techniques in women with PCOS, revealed more cycle cancellation and that the duration of stimulation cycles was significantly longer in women with PCOS.⁴⁹ There is evidence that the use of metformin improves viable pregnancy rates and reduces the incidence of OHSS.⁵⁰ The success of IVF techniques is similar to that of patients

without PCOS, which implies that PCOS does not intervene in embryo implantation.

Treatment of menstrual dysfunction

Chronic anovulation is associated with an increased risk of endometrial hyperplasia and carcinoma.⁵¹ Thus, it is prudent to consider endometrial biopsy in patients with PCOS who have not had menstrual bleeding for a year or longer. Some investigators have advocated the use of ultrasonography to determine endometrial thickness in deciding whether to do a biopsy of the endometrium. Endometrial proliferation can be inhibited by administering either cyclic progestin or oral contraceptives with a combination of estrogen and progestin. The latter approach, which also reduces ovarian androgen production, may be particularly beneficial in this setting.

Treatment of androgen-related symptoms

The over-riding androgenic symptoms that the individual presents will vary from patient to patient; for some it is mainly hirsutism, but for others it is acne and/or alopecia. Many have both hirsutism and acne, and a few complain of significant acne, hirsutism, and alopecia.⁵²

Hirsutism

Overall, 70%–80% of women with excess androgen demonstrate hirsutism, usually defined as a Ferriman–Gallwey score of at least 8, although this prevalence is less in certain ethnic groups, such as East Asians, who may have fewer hair follicles endowed per unit area of skin.⁵³ Androgens increase the growth rate of hair and transform vellus hair to terminal hair. Reduction of androgens reduces new hair growth and slows the growth of terminal hair that is already present.⁵⁴ Hair grows in nonsynchronous cycles. The growth or anagen phase varies according to body area and is ~4 months for facial hair. Given this long hair growth cycle, the effects of hormonal therapy require more than 6 months to be maximal.

Oral contraceptive pills

In women who have no desire to conceive, they can be treated with oral contraceptive pills (OCPs). OCPs reduce hyperandrogenism by promoting direct negative feedback on LH secretion, which results in decreased ovarian synthesis of androgens. Further, they increase liver production of sex hormone-binding globulin and subsequently decrease circulating free androgen. Other mechanisms include reduction in adrenal androgen secretion and inhibition of peripheral conversion of testosterone to dihydrotestosterone and binding of dihydrotestosterone to androgen receptors.⁵⁵ The choice

of oral contraceptive is important, because most progestins also possess variable androgenic effects. Available low-dose OCPs (defined as $<50 \mu\text{g}$) contain ethinyl estradiol in doses ranging from $15 \mu\text{g}$ to $35 \mu\text{g}$. An important consideration for the progestin component is the degree of androgenicity of the progestin.⁵⁶ Newer OCPs contain fewer androgenic progestins (such as norethindrone, desogestrel, and norgestimate), and two progestins (cyproterone acetate [CPA], which is used in low doses in OCPs, and drospirenone) function as androgen receptor antagonists, CPA being more potent in its effect. CPA may also inhibit $5\text{-}\alpha\text{-reductase}$ activity, decreasing the availability of the more potent androgen, dihydrotestosterone.⁵⁷ A third antiandrogenic progestin, dienogest, has recently become available in Europe and is combined with estradiol as an OCP. One of the newest OCPs that might be more effective in reducing the growth of new terminal hair and acne formation is a formula that contains a combination of nonandrogenic progestin, drospirenone, and ethinyl estradiol; thus, it is potentially ideal for the treatment of women with PCOS. Drospirenone is a spironolactone analog with mineralocorticoid activity; as a result, it has some diuretic property. However, it should not be prescribed to those predisposed to hyperkalemia. Treatment must be given for at least 6–9 months before improvement in hirsutism can be seen.⁵⁶

Estrogen–progestin combination therapy (with the use of a combination OCP) remains the predominant treatment for hirsutism and acne in PCOS.⁴ Controversy persists regarding the use of OCPs as first-line therapy in women with PCOS. These agents clearly improve hirsutism and acne and protect against unopposed estrogenic stimulation of the endometrium, but their potential adverse effects on insulin resistance, glucose tolerance, vascular reactivity, and coagulability are a concern, particularly now that insulin-lowering agents are available.

Antiandrogens

Antiandrogens such as spironolactone, CPA, or flutamide act by competitive inhibition of androgen-binding receptors or by decreasing androgen production.⁵⁸

Spironolactone, which is an aldosterone antagonist, is a dose-dependent competitive inhibitor of the androgen receptor and can also inhibit $5\text{-}\alpha\text{-reductase}$ activity. Spironolactone possesses moderate antiandrogenic effects when administered in large doses ($100\text{--}200 \text{ mg}$ daily). It has demonstrable effects on hirsutism over and above those induced by OCPs.⁵⁹ Although generally well tolerated, it occasionally causes fatigue, postural hypotension, and dizziness, and when administered alone in high doses, it may

cause menstrual irregularity. The risk of feminizing a male fetus, if pregnancy occurs, precludes its use as monotherapy in sexually active women with PCOS. Spironolactone and oral contraceptives appear to be synergistic.⁶⁰ Thus, it is often used with OCPs.

CPA is a progestational antiandrogen. CPA competitively inhibits the binding of testosterone and its more potent conversion product $5\alpha\text{-dihydrotestosterone}$ to the androgen receptor. Used in high doses ($50\text{--}100 \text{ mg}$) and in a reverse sequential regimen (for the first 10 days of cycle), in combination with ethinyl estradiol $20\text{--}50 \mu\text{g}$ (to ensure regular menses), it was shown to be more effective than finasteride, a $5\text{-}\alpha\text{-reductase}$ inhibitor.⁶¹ CPA is generally well tolerated, although it may cause headaches, nausea, weight gain, breast tenderness, loss of libido, and, rarely, hepatotoxicity effects. As with spironolactone, there is a risk of feminizing a male fetus. A combination of ethinyl estradiol and CPA is very effective in treating hirsutism and acne. Apart from its antiandrogenic effect, CPA has a marked progestational property preventing ovulation.⁶² Loss of hair, which frequently accompanies seborrhea, also improves. Frequent monitoring of liver and renal function is necessary during therapy with antiandrogens. Similar to that with OCP, improvement of hirsutism is expected to be noticeable after 6 months of treatment. Although there is a considerable variation among individuals, the maximum effect is usually seen after 9–12 months of antiandrogen treatment.

Flutamide is a nonsteroidal, selective antiandrogen without progestogenic effect. It is marketed for the treatment of prostate cancer and is very effective in treating hirsutism. In a dose of 500 mg daily, it was found to be similarly effective as spironolactone 100 mg in women with idiopathic hirsutism, and, in a recent study, the minimal effective dose was found to be 125 mg daily. Its major concern is serious hepatotoxicity, although doses up to 375 mg have been used without any significant hepatotoxicity.⁶³ However, it is rarely used alone due to its high cost and the risk of hepatocellular toxicity. Recent studies have indicated that a combination of flutamide 62.5 mg daily with metformin 850 mg daily is more effective in improving symptoms of PCOS than OCP alone.⁶⁴

Finasteride is a type 2 ($5\text{-}\alpha\text{-reductase}$) activity inhibitor that inhibits the production of dihydrotestosterone. Enhanced $5\text{-}\alpha\text{-reductase}$ activity in hirsutism probably involves both type 1 and type 2 enzymes, so it is unlikely to be an optimal treatment. Hirsutism scores were lower in studies of finasteride.⁶⁵ Comparison of finasteride with spironolactone has shown equal or lesser efficacy of finasteride. Finasteride has also been used in combination with a CPA-containing OCP,

and the addition of finasteride 5 mg to the OCP was shown to be better than the OCP alone.⁶⁶ When finasteride was compared directly with an OCP-containing low-dose CPA, the effect was equivalent. Although finasteride has a low side effect profile, its feminizing effects on a male fetus preclude its use in most patients. Due to the risk of feminization of a male fetus, pregnancy must be avoided during treatment with all antiandrogens.⁶⁷

Glucocorticoids

Some women with PCOS have elevated adrenal androgen levels, although their contribution to ovulatory dysfunction appears modest.⁶⁸ Glucocorticoids suppress adrenal androgen secretion and have been used in patients with adrenal hyperandrogenism. Their use is most legitimate in patients with classic congenital adrenal hyperplasia, where they can help prevent and manage hirsutism and allow ovulatory cycles. In nonclassic congenital adrenal hyperplasia and functional adrenal androgen excess (a minority of PCOS patients), their role is more limited.⁶⁹ Suppression of adrenal androgens results in a minor improvement of hirsutism, although prolonged remission after therapy withdrawal can be obtained. A trial of CPA versus hydrocortisone in patients with late-onset congenital adrenal hyperplasia showed a greater decrease in hirsutism scores with 1 year of CPA compared with hydrocortisone (54% vs 26%). These results occurred despite a greater reduction of androgens with glucocorticoids, highlighting the importance of peripheral receptivity to androgens.⁷⁰ Overdosing can occur, leading to adrenal atrophy, weight gain, and decreased bone mineral density. Glucocorticoid (5–7.5 mg of prednisone once or twice daily) has been shown to improve hirsutism in women with congenital adrenal hyperplasia. However, its effect on hirsutism due to other causes is unclear.⁶⁵ Unless a woman with PCOS has marked adrenal androgen excess, prolonged use of glucocorticoids is not advised.

Gonadotropin-releasing hormone agonist

Gonadotropin-releasing hormone agonist (GnRHa) is effective even in women with severe insulin resistance who are unresponsive to OCP.⁷¹ GnRHa suppresses pituitary hormones, decreases androgen and estradiol secretion, and improves severe forms of hirsutism. To avoid problems associated with estrogen deficiency, ‘add-back’ therapy with estrogen–progesterone or low-dose OCP is advisable. However, this method of treatment is expensive, limiting its use to severe forms of ovarian hyperandrogenism with hyperinsulinemia.

Insulin-lowering agents

Both metformin and thiazolidinediones may lower ovarian androgen secretion, mainly through their insulin-lowering effects. In a Cochrane Database Systematic Review article, limited data on small numbers of patients have shown no evidence of a difference in effect between metformin and OCPs on hirsutism and acne.⁷² Some effects of rosiglitazone on hirsutism were shown by Yilmaz et al and troglitazone (no longer available) improved hirsutism in women with PCOS.⁷²

Direct hair removal

Electrolysis has been used for many years to remove unwanted hair. A fine needle is inserted into the hair follicle, and an electrical current is applied. Erythema and postinflammatory pigment changes may occur, and scarring is possible.⁷³ Photoepilation uses laser and nonlaser light sources to damage hair follicles, but vellus hair remains and can be converted to terminal hair. Although laser treatment is more expensive, it is less painful and much faster.⁷⁴ There is potential for depigmentation and scarring with laser use, especially in darker-skinned women.

Topical treatment

Eflornithine hydrochloride, an inhibitor of the enzyme ornithine decarboxylase in human skin, has been approved for topical use in treating facial hirsutism, taking 6–8 weeks for its effect to be apparent.⁷⁵ It can be combined with laser treatment.

Combination therapy

In the Endocrine Society Practice Guidelines discussing the evaluation and treatment of hirsutism in premenopausal women, it was recommended that OCPs or direct hair removal be used initially.⁷⁶ Then, if at least 6 months of OCP therapy has not significantly decreased the rate of hair growth, antiandrogens may be added.

Acne

Both OCPs and antiandrogens have been used successfully in the treatment of acne.⁷⁷ Within 3–6 months of OCP treatment, inflammatory acne counts are reduced by 30%–60%, with improvement in 50%–90% of patients. OCPs are especially useful in patients with deep-seated nodules and helpful in patients relapsing on isotretinoin.

Alopecia

There are no extensive trials for alopecia, but OCPs and androgen blockers are usually administered. In limited studies, CPA has had some effect, as has finasteride.⁷⁸

Alternative medicine and PCOS

Absence of evidence is not evidence of absence. Alternative medicine has been emerging as one of the commonly practiced medicines for different health problems. Alternative medicines include many modalities, such as kinesiology, herbalism, homeopathy, reflexology, acupressure, acupuncture, and massage therapy. Acupuncture is the most common modality. The benefit acupuncture seems to have for PCOS sufferers is in helping them regulate and manage their periods. However, it has also been shown to aid in weight loss and reducing headaches as well as improving patients' moods and outlooks. Women with PCOS will have needles placed along the acupuncture meridians related to the reproductive system. This will help stimulate the organs, improve blood flow to the area, contribute to normalizing hormone levels, and promote the proper functioning of the reproductive system.

Because it is only in the last 20 years or so that acupuncture has started to be widely practiced in the West, few studies have been performed on women with PCOS receiving acupuncture. In 2000, a study was carried out by researchers at Göteborg University in Sweden involving 24 women with PCOS who received acupuncture for 2–3 months. At the end of the study, nine women (38%) had regular ovulation. However, the study also found that those women with more severe PCOS cases, particularly those participants who had high testosterone and insulin levels and were obese, did not have any luck with the acupuncture treatment.⁷⁹ Recently, a randomized controlled trial proved the efficacy of electroacupuncture in treating women with PCOS.⁸⁰

In conclusion, it is clear that PCOS is an enigma. Its underlying pathophysiology is not fully understood. No treatment is a panacea, because treatments, so far, have been directed at the symptoms but not at the syndrome itself. Extensive efforts should be made to fully investigate the syndrome in order to make therapy more successful and to delay the serious long-term effects of the disease on patients' health.

Disclosure

The authors report no conflicts of interest in this work.

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