Pharmacologic Treatment of Polycystic Ovary Syndrome

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ABSTRACT

Women with polycystic ovary syndrome (PCOS) most often seek treatment for reduction of hair growth and/or acne, restoration of menstrual cyclicity, and infertility. In addition, these patients are increasingly seeking advise and treatment for the metabolic abnormalities related to PCOS (e.g., insulin resistance and type 2 diabetes). In this review, we outline the pathophysiologic events underlying the cutaneous manifestations of androgen excess and provide a rationale for use of the various pharmacologic agents available for treatment. Options for the treatment of the reproductive abnormalities (menstrual dysfunction and interfility) are presented. Finally, the metabolic manifestations of PCOS are reviewed and their treatment is discussed.

KEYWORDS: Polycystic ovary syndrome, hirsutism, oligomenorrhea, insulin resistance, type 2 diabetes mellitus

Women with polycystic ovary syndrome (PCOS) most often seek treatment for reduction of hair growth and/or acne, restoration of menstrual cyclicity, and infertility. In addition, these patients are increasingly seeking advice and treatment for the metabolic abnormalities related to PCOS (e.g., insulin resistance and type 2 diabetes). It is therefore important to develop a "problem-oriented" approach to the treatment of the patient with PCOS (Table 1).

TREATMENT OF HIRSUTISM AND ACNE

Medical treatment of hirsutism and/or acne in PCOS generally involves reduction of androgen levels or their end-organ effects. This is usually accomplished by (1) suppression of adrenal and/or ovarian androgen production, (2) alteration of binding of androgens to their plasma binding proteins, (3) impairment of the peripheral conversion of androgen precursors to active androgen, and (4) inhibition of androgen action at the target tissue level.

Combination estrogen-progestin therapy, in the form of an oral contraceptive, remains the mainstay of treatment for hirsutism and acne. Most oral contraceptives contain either ethinyl estradiol or mestranol as the estrogenic component. The estrogenic component is primarily responsible for the suppression of luteinizing hormone (LH) and thus serum androgen levels and also results in a dose-related increase in levels of sex hormone–binding globulin (SHBG). Raising SHBG levels results, in turn, in a lowering of the fraction of plasma testosterone that is "free" or unbound, thus lowering the proportion of hormone that can bind to the androgen receptor. Combination estrogen-progestin therapy has been demonstrated to decrease dehydroepiandrosterone sulfate (DHEAS) levels, possibly by reducing adrenocorticotropic hormone (ACTH) levels. Estrogens also have a direct, dose-dependent suppressive effect on sebaceous cell function.

A key determinant in the choice of a specific oral contraceptive is the type of progestin contained within

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Table 1 Pharmacologic Therapy of Polycystic Ovary Syndrome

Agent	Mechanism(s) of Action	Examples	Use(s)*
Combination estrogen-progestins	Increase SHBG; suppress LH and FSH; suppress	Ortho-Cyclen Ortho-Cept	1, 2
	As above with a progestin that acts as antiandrogen	Yasmin	
Antiandrogens	Inhibit androgens from binding to the androgen receptor	Cyproterone acetate Spironolactone Flutamide	1
GnRH agonists	Down-regulation of GnRH secretion	Leuprolide Nafarelin	1
Glucocorticoids	Suppress ACTH and thus adrenal androgen production	Prednisone Dexamethasone	1, 2, 3
5α-Reductase inhibitors	Inhibition of 5α-reductase	Finasteride	1
Ornithine decarboxylase inhibitors	Inhibition of ornithine decarboxylase	Vaniqa (topical)	1
Clomiphene citrate	Antiestrogen; acts to induce rise in FSH, LH	Clomid	3
Human recombinant FSH plus hCG	Follicular recruitment and maturation	Puregon, Follistim	3
Biguanides	Reduce hepatic glucose production, secondarily lowering insulin levels. ?Direct effects on ovarian steroidogenesis	Metformin (Glucophage, Glucophage XR)	1, 2, 3, 4
Thiazolidinediones	Enhance insulin action at target tissue level (adipocyte, muscle) Some evidence for direct effects upon ovarian steroidogenesis	Rezulin† Pioglitazone (Actos) Rosiglitazone (Avandia)	1, 2, 3, 4
D-*chiro*-Inositol	Enhanced insulin action	Not applicable	2, 3, 4

*1, Hirsutism and/or acne; 2, oligo/amenorrhea; 3, ovulation induction; 4, insulin-lowering therapy.
†Not available.
ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; SHBG, sex hormone–binding globulin.

the compound. Each progestin varies in its suppressive effect on SHBG levels as well its androgenic potential. Ethynodiol diacetate has a relatively low androgenic potential, whereas progestins such as norethindrone, norgestrel, and levonorgestrel are particularly androgenic.

Norgestimate and desogestrel exemplify newer progestins that are virtually nonandrogenic.[1] These agents have been the progestins of choice in treatment of women with PCOS. More recently, drospirenone, an analogue of spironolactone that is unique in that it has both antimineralocorticoid and antiandrogenic activities,[2] has been approved for use as the progestational agent in combination with ethinyl estradiol. As such, it holds the potential for use in the treatment of women with PCOS.

The maximal effect of oral contraceptives on acne is usually observed by 2 months. In contrast, the effect on hair growth may not be evident for up to 6 months and the maximum effect requires 9 to 12 months owing to the length of the hair growth cycle.

Cyproterone acetate acts mainly by competitively inhibiting binding of testosterone and dihydrotestosterone to the androgen receptor.[3] Although not available for use in the United States, cyproterone acetate is an effective treatment for hirsutism and acne[4,5] and is used throughout Canada, Mexico, and Europe. Side effects include irregular uterine bleeding, nausea, headache, fatigue, weight gain, and decreased libido.

Spironolactone appears to be as effective as cyproterone acetate when administered in large doses (100 to 200 mg daily).[6,7] It is a potent antimineralocorticoid that was developed as a progestational analogue. It has relatively few side effects; hyperkalemia and hypotension are possible but infrequently observed. Its major side effect is menstrual irregularity when used alone; for this reason, estrogen-progestin can be given in conjunction with spironolactone.[8,9] Use of estrogen-progestin in conjunction with spironolactone may also be important to prevent pregnancy because of the risk of the compound causing feminization of a male fetus.

Flutamide is a potent nonsteroidal antiandrogen without progestational, estrogenic, corticoid, antigonadotropic, or androgenic activity.[10] Data have accumulated to support its efficacy in the treatment of hirsutism.[11] Concerns about the induction of hepatocellular dysfunction, however, have limited its use.

Gonadotropin-releasing hormone (GnRH) agonists have been reported to be effective in the treatment of

hirsutism.[12,13] Their chronic administration suppresses pituitary-ovarian function, thus inhibiting both ovarian androgen and estrogen secretion. Because of the concomitant reduction of serum estrogen levels and the measurable reductions in bone mineral density observed when GnRH agonists are used alone,[14,15] it appears unwise to use these agents for longer than 6 months. It has been suggested that "add-back" therapy in which combination estrogen-progestin is prescribed in conjunction with a GnRH agonist may be effective in treating androgen excess without the side effects of hypoestrogenemia.[16]

Adrenal androgens are more sensitive than cortisol to the suppressive effects of glucocorticoids.[17] Although glucocorticoids have been reported to restore ovulatory function in PCOS, the extent to which this occurs is highly variable.[18,19] Unless there is a major adrenal androgen source, prolonged use of glucocorticoids is not advised.

Finasteride, a 4-aza-steroid, is a competitive inhibitor of type 2 5α-reductase.[20] Although beneficial effects on hirsutism have been reported,[21] the prominence of type 1 5α-reductase in the pilosebaceous unit makes it unlikely to be an optimal form of treatment.

Finally, eflornithine, in the form of a topical cream (Vaniqa; Bristol-Myers Squibb), has been approved for use in treating facial hirsutism. Apparent benefit has been reported when the compound is applied to the affected areas of the face, twice daily, for 8 weeks. Topical eflornithine directly inhibits the enzyme ornithine decarboxylase in human skin, thereby inhibiting cell growth, polyamine synthesis, and ultimately the rate of hair growth. Its primary action is one of hair growth inhibition; it is not a depilatory.

TREATMENT OF OLIGO/AMENORRHEA AND INFERTILITY

Chronic oligo/anovulation results in persistent stimulation of endometrial tissue by estrogen (mainly estrone). In the setting of PCOS, without the progesterone-induced inhibition of proliferation and differentiation to secretory endometrium that occurs after ovulation, there is an increased risk for endometrial hyperplasia and carcinoma.[22] A threefold increased risk of endometrial cancer in anovulatory women has been reported.[23] Although 5% or fewer of endometrial cancers occur in women under the age of 40 years, the majority have PCOS.[24] Thus, anovulatory women with PCOS are recommended to take progestins to reduce the risk of endometrial hyperplasia or carcinoma.

An endometrial biopsy is suggested if a patient has been anovulatory for a year or more[25]; ultrasonography may help to establish risk and need for biopsy. If a progestin is used, it should be given for 12 to 14 days every month to minimize the risk of endometrial hyperplasia.[26,27] The combined estrogen-progestin oral contraceptive pill is particularly beneficial in women with PCOS in that it both inhibits endometrial proliferation and reduces ovarian androgen production, thus ameliorating the consequences of hyperandrogenism.

Clomiphene citrate remains the first line of therapy for ovulation induction in women with PCOS.[28,29] The usual regimen is 50 mg/day for 5 days beginning on cycle day 3 to 5 following spontaneous or progestin-induced bleeding. The dose can be increased by 50 mg per day (usually to a maximum dose of 200 mg/day) in subsequent cycles if ovulation does not occur (serum progesterone in the luteal phase remains less than 3 ng/mL). Using a graduated regimen of 50 to 200 mg daily for 5 days, ovulation can be induced in about 80% of oligomenorrheic women, of whom approximately half conceive. In women without other infertility factors, about 88% of those ovulating eventually conceive with a monthly fecundity rate of 0.22, which is similar to that of fertile women discontinuing the diaphragm.[30] There is a 15% spontaneous abortion rate and a 4% incidence of twins[30,31] associated with the use of clomiphene citrate. Metformin has been reported to reduce the rate of spontaneous pregnancy loss in PCOS (see later).[32]

The PCOS patients who do not respond to clomiphene therapy usually require either low-dose human recombinant follicle-stimulating hormone (FSH) or surgically induced ovulation (i.e., ovarian diathermy). In hyperinsulinemic women with PCOS, lowering insulin levels with either drugs or weight loss may also induce ovulation (see later).

There is no clinical advantage of human menopausal gonadotropins (hMGs) over FSH for induction of ovulation in women with PCOS.[33] In PCOS, stimulation is initiated with 75 IU/day instead of the standard 150 IU, and patients are maintained on this dose for 1 to 2 weeks. This lower dose lowers the risk of ovarian hyperstimulation syndrome. Gonadotropins are increased at 0.5 ampule increments (37.5 IU) every 7 days if no follicular growth occurs at the initial dose as determined by ultrasonography. Compared with standard gonadotropin therapy, low-dose therapy with either FSH or hMG in PCOS results in a higher rate of single dominant follicle development, fewer ovulatory follicles at the time of human chorionic gonadotropin administration, and lower mean estradiol levels.[34–38] Reducing the FSH dose as follicular size increases may further increase the likelihood of monofollicular development.[39,40]

With low-dose gonadotropin therapy about 95% of patients ovulate with a 55% cumulative pregnancy rate after six cycles.[41] Multiple gestation occurs in only 6% of pregnancies. However, spontaneous abortion rates range from 20 to 35%.[37,41] Down-regulating the pituitary-ovarian axis with GnRH agonist prior to initiation of gonadotropin therapy may

decrease the likelihood of spontaneous abortion,[42,43] but this has never been confirmed in a randomized trial.

There has been renewed interest in surgically inducing ovulation in women with PCOS using laparoscopy and electrocautery or laser to produce multiple burns in the ovarian capsule. A review of 1124 patients found spontaneous ovulation in 77% and pregnancy in 49% of patients.[44] Most patients ovulated spontaneously following laparoscopic ovulation induction, but some required clomiphene citrate or gonadotropins, which increased the total pregnancy rate to 60%. In PCOS patients with only anovulation and no other infertility factors, a cumulative pregnancy rate of 80%, with about 80% of conceptions occurring within the first 8 months after surgery, has been reported.[45] In contrast to results with gonadotropins, the spontaneous abortion rate after a laparoscopic ovulation induction is only about 15% and multiple pregnancies are uncommon (2.5%).[44,46]

As noted, lowering insulin levels with either weight loss or drugs may induce ovulation in obese, hyperinsulinemic women with PCOS. A modest weight loss of 5 to 10% results in return to regular menses or pregnancy in up to 80% of obese women with PCOS.[29,47] Both metformin and troglitazone have been reported to restore regular menses and induce ovulation in women with PCOS.[48–50] In a randomized trial, obese women with PCOS were significantly more likely to ovulate if they received 1500 mg of metformin daily (34%) rather than placebo (4%; $p < 0.001$) for 35 days.[51] Of the subjects who remained anovulatory after 35 days, the metformin-treated subjects were significantly more likely to ovulate following clomiphene treatment than the placebo-treated subjects (90 versus 8%; $p < 0.001$). When troglitazone was administered to women with PCOS either alone or in conjunction with clomiphene citrate, there was a significant enhancement in ovulatory function.[49] Specifically, the ovulation rate per cycle increased from 34.9% with clomiphene citrate alone to 72.7% when troglitazone was coadministered.

Finally, a multicenter study[50] in which 305 premenopausal women with PCOS were randomly assigned to treatment with placebo (PBO) or troglitazone (150, 300, or 600 mg/day) revealed that ovulatory rates were significantly greater for patients receiving 300 and 600 mg than for those receiving placebo. Of PCOS patients treated with 600 mg, 57% ovulated over 50% of the time compared with 12% of placebo-treated patients. Thus, troglitazone improved the ovulatory dysfunction of PCOS in a dose-related fashion, with a minimum of adverse effects. Although ovulation induction with insulin-lowering therapy has been promising, especially in obese PCOS patients, pregnancy rates and long-term outcomes with such agents remain unknown.

TREATMENT OF ASSOCIATED METABOLIC ABNORMALITIES: INSULIN RESISTANCE AND GLUCOSE INTOLERANCE

As discussed earlier, hyperinsulinemia is a key component in the pathogenesis of PCOS. This realization has provided the basis for advances in treatment strategies for women with the disorder. Weight reduction, when it can be achieved, is still an important component in the treatment of PCOS. However, not all women with PCOS are obese, and because the etiology of obesity in PCOS in not known, there is currently no effective manner to target this problem in PCOS. Pharmacologic reduction in insulin levels appears to offer another therapeutic modality for PCOS and is one that may ameliorate the sequelae of both hyperinsulinemia and hyperandrogenemia.

At least five different modalities have been used to lower insulin levels in PCOS. These include weight loss, diazoxide, and more recently metformin, the thiazolidinediones (pioglitazone and rosiglitazone; troglitazone is no longer available for use), and D-*chiro*-inositol.

Both metformin and the thiazolidinediones effect reductions in insulin levels, but they do so by fundamentally different mechanisms. Metformin is a disubstituted biguanide that, when administered to obese or lean subjects with type 2 diabetes, appears to reduce fasting glucose concentrations as well as improve oral glucose tolerance. This improved glucose tolerance usually occurs with a modest reduction of concomitantly measured plasma insulin levels. Although there is some modest improvement in glucose disposal rate with metformin, the primary mechanism of action appears to be its effect on reducing hepatic glucose output.[52]

The thiazolidinediones are a class of antidiabetic drugs that improve the action of insulin in the liver, skeletal muscle, and adipose tissue. These compounds act primarily as ligands for the nuclear peroxisome proliferator activated receptor γ (PPAR-γ), which, when activated, enhances transcription of a host of factors that promote glucose disposal in fat and muscle. Numerous human studies have demonstrated that thiazolidinediones improve both fasting and postprandial hyperglycemia in subjects with type 2 diabetes. In contrast to the effects observed with metformin, the thiazolidinediones have a major impact on glucose disposal rate, with a modest effect on hepatic glucose output. As such, the thiazolidinediones are most appropriately viewed as true insulin-sensitizing agents.

The first study in which metformin was administered to test the hypothesis that androgen reduction follows from insulin reduction was that of Velazquez et al.[48] In that study, metformin was administered to 26 women with PCOS (500 mg three times daily for 8 weeks) and resulted in a significant reduction in total testosterone, free testosterone, and free androgen index as well as a significant rise in SHBG in comparison

with pretreatment levels. These changes were associated with reductions in insulin responses to oral glucose administration and in the "insulogenic index" (defined as the ratio of insulin to glucose response after oral glucose administration). It is important to note that the subjects in this study lost weight, which was a likely contributor to the reduction in insulin secretion on repeated oral glucose tolerance test (OGTT). As a result, the effect of metformin upon insulin secretion could not be clearly separated from that of weight loss.

To circumvent the confounding effects of weight reduction on both insulin secretion and androgen levels, we treated 14 obese, nondiabetic women with PCOS with metformin for a 3-month period during which body weight was maintained and compared their ability to respond to oral and intravenous glucose challenges before and after treatment. In addition, we examined the ovarian steroidogenic response to leuprolide before and after metformin. We found that both the glucose and insulin responses to an oral glucose challenge and the profound insulin resistance of obese women with PCOS were not improved by metformin.[53] These findings were in contrast to those of Nestler and Jakubowicz,[54] who found, in a study of similar design, that the area under the serum insulin curve decreased by 53% after oral glucose administration and was associated with a reduction in both the basal and leuprolide-stimulated serum 17-hydroxyprogesterone concentration. None of these values changed significantly in women who received placebo. A number of additional studies have been published that examine the effects of metformin in women with PCOS as reviewed by Nestler et al.[55]

As discussed previously, metformin has been administered to obese women with PCOS in an attempt to determine whether the ovulatory response to clomiphene would be enhanced by reduction in insulin levels (see earlier). In this study, 61 women with PCOS (one half of whom who had been previously treated with clomiphene without response) were randomly assigned to receive either placebo or metformin (500 mg twice daily) for 1 month. Women who did not ovulate spontaneously, as defined by a serum progesterone above 8 ng/mL, were then given 50 mg of clomiphene daily for 5 days while continuing to take metformin or placebo. Among those who received metformin plus clomiphene, there was a significant ($p = 0.03$) reduction in the mean area under the serum insulin curve after oral glucose administration from 6745 ± 2021 to 3479 ± 455 μU/mL per minute, which was associated with an ovulatory response rate of 90% compared with an 8% response rate in those who took placebo in concert with clomiphene ($p < 0.001$). Of note, however, was the lack of reduction in free testosterone in the metformin-treated group. One may infer from these results that metformin could act to enhance ovulation without changing the steroid milieu.

Although fewer studies have been performed using the thiazolidinediones in PCOS, the results of these studies have been highly consistent. Dunaif et al[56] have documented that improvement of insulin resistance by administration of troglitazone, an insulin-sensitizing agent in the thiazolidinedione class of drugs, results in attenuation of hyperinsulinemia and hyperandrogenemia in obese women with PCOS. This improvement in insulin sensitivity was reflected in a reduction of the fasting insulin concentration, 2-hour insulin concentration, and integrated insulin response to a 75-g oral glucose challenge. In addition, there was a significant improvement in the insulin sensitivity index (S_i) derived from a rapidly sampled intravenous glucose tolerance test.

We[57] administered troglitazone to 13 obese women with PCOS and impaired glucose tolerance to determine whether attenuation of hyperinsulinemia ameliorates the metabolic abnormalities of the syndrome. Before and after treatment with troglitazone, 400 mg daily for 12 weeks, all had a GnRH agonist (leuprolide) test, an OGTT, a frequently sampled intravenous glucose tolerance test (IVGTT), an oscillatory glucose infusion to assess beta cell function, and measures of fibrinolytic capacity, including plasminogen activator inhibitor type 1 (PAI-1). There was no change in body mass index or body fat distribution after treatment. Both the fasting (91 ± 3 versus 103 ± 3 mg/dL; $p < 0.001$) and 2-hour (146 ± 8 versus 171 ± 6 mg/dL; $p < 0.02$) plasma glucose concentrations during the OGTT declined significantly. Insulin sensitivity improved significantly. Basal levels of total testosterone and free testosterone declined significantly after troglitazone treatment, as did leuprolide-stimulated levels of 17-hydroxyprogesterone, androstenedione, and total testosterone. Beta cell function also improved as reflected by an enhanced ability to "entrain" insulin secretion in response to an oscillatory glucose infusion. Decreased functional activity of PAI-1 in blood was also observed.

The realization that hyperinsulinemia is a key component in the pathogenesis of PCOS has thus provided the basis for these advances in treatment strategies for women with the disorder. Weight reduction, when it can be achieved, is still an important component in the treatment of PCOS. However, not all women with PCOS are obese, and because the etiology of obesity in PCOS in not known, there is currently no effective manner to target this problem in PCOS. Pharmacologic reduction in insulin levels appears to offer another therapeutic modality for PCOS and is one that may ameliorate the sequelae of both hyperinsulinemia and hyperandrogenemia. However, additional studies and long-term follow-up of patients so treated are necessary before these agents can be considered first-line treatment for PCOS.

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