Advances in Treatment Options for Polycystic Ovary Syndrome

Sanam Lathief, MD[1] and Lubna Pal, MBBS, MRCOG, MS[2]

1. Resident, Internal Medicine, Hospital of Saint Raphael, New Haven, Connecticut; 2. Associate Professor and Director,
Program for Polycystic Ovarian Syndrome and Director, Program for Reproductive Aging and Bone Health,
Yale Reproductive Endocrinology, Yale University School of Medicine, New Haven, Connecticut, US

Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy seen in women of reproductive age. Clinical concerns relating to PCOS range from ovulatory infertility and menstrual disorders to risk of diabetes and cardiovascular disease. Hormonal contraceptives have been the mainstay of the management of common PCOS symptoms, such as menstrual irregularity and clinical stigmata of androgen excess (i.e., hirsutism and acne). An appreciation of the relevance of metabolic pathways in the pathophysiology of PCOS is relatively recent, and has translated into an expansion of the therapeutic strategies available for the management of PCOS. Insulin sensitizers were one of the first metabolic modulators to be incorporated in the clinical management paradigm, albeit with mixed results. Recognizing that insulin resistance is central to the pathophysiology of PCOS, newer agents—e.g., thiazolidinediones— followed, with almost comparable efficacy to metformin. Statins and most recently incretins constitute novel therapies with distinct metabolic targets that seem to hold promise in the management of PCOS. In tandem with the expansion in pharmaceuticals, a host of complementary and alternative medical therapies have generated interest for purported promise in the management of PCOS, including vitamin D, acarbose, and myo-inositol. The therapeutic options for managing PCOS-related infertility have also expanded. Clomiphene citrate (CC) has long been the first-line strategy for ovulation induction in the setting of anovulatory infertility; however, aromatase inhibitors are fast gaining acceptance as an ovulation induction strategy, with results comparable or even better than those seen with CC. An increasing level of therapeutic sophistication is reflected in ovarian stimulation protocols judiciously using gonadotropins, gonadotropin-releasing hormone antagonists, the procedure of ovarian drilling, and assisted reproductive technologies with *in vitro* oocyte maturation.

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age, with an approximate prevalence of 6–10 %.[1–3] Characterized by clinical features of hyperandrogenism (such as hirsutism) and/or biochemical androgen excess and ovulatory dysfunction, PCOS is additionally associated with a spectrum of comorbidities that include infertility, increased risk of type 2 diabetes and of cardiovascular disease (CVD), psychological burden, and risk of endometrial pathologies including endometrial cancer.[2–4] The therapeutic approach to PCOS entails a focus on the overt presenting complaint(s) (e.g., oligomenorrhea, clinical hyperandrogenism, ovulatory infertility) as well as on the metabolic burden that predisposes this patient population to a spectrum of comorbidities in the long run, including type 2 diabetes and CVD. In this article, the authors have attempted to provide an overview of the treatment options that offer therapeutic benefit in PCOS.

Treatment Options for Targeting Common Symptoms
Combined Oral Contraceptives

Having long been used as the first-line treatment in PCOS management, combined oral contraceptives (COCs) offer not just menstrual regulation and endometrial protection, but also a benefit against cutaneous stigmata of hyperandrogenism in women with PCOS.[5–7] Mechanisms whereby COCs mediate improvements in PCOS-related symptoms include:

- a suppression of pituitary luteinizing hormone (LH), thereby reducing the stimulant effect of LH on androgen production by the ovarian theca cells;
- an increase in hepatic sex hormone binding globulin (SHBG) directly resulting from the estrogen component in the COC; the net effect is a

decline in the free androgen levels and hence an improvement in the clinical features of hyperandrogenism (e.g., acne and hirsutism); and

- the antiproliferative effects of the progestin component of the COC formulation, which offers protection against proliferative endometrial pathologies that oligomenorrheic and insulin-resistant women are particularly at risk of.

The attainment of a predictable withdrawal bleeding pattern with the use of COCs is influenced to some extent by the dose of estrogen and type of progestin in the COC formulation. COC-related improvements in acne may be evident within weeks of initiating therapy, whereas any benefit against excess hair growth is slow to appear. While all available COC formulations are likely to offer a degree of cutaneous benefit, the inclusion of certain synthetic progestin formulations with innate antiandrogenic properties, such as drosperinone and cyproterone acetate, may offer additional advantages in terms of acne control.[5–7]

Progesterone-only Approach

In oligomenorrheic women, particularly in those with excess body mass, the use of progestins alone (when administered orally or via intramuscular, subcutaneous, or intrauterine delivery routes) can be efficacious in mitigating the risk of endometrial pathologies (such as endometrial hyperplasia and cancer) that are recognized in the setting of chronic annovulation and long-term exposure to unopposed estrogen (endogenous or exogenous). The successful use of intrauterine progesterone-releasing systems in cases of endometrial hyperplasia and early stages of endometrial cancer has also been described.[8,9] Annovulatory and oligomenorrheic women who are deemed at a disproportionately higher risk of estrogen-related risks (such as thromboembolism) may thus benefit from a progestin-only approach,[10] as a strategy for managing the commonly encountered dysfunctional uterine bleeding and as prophylaxis against the risk of endometrial cancer.

Treatment Options for Managing Infertility

Impaired functioning of the hypothalamic–pituitary–ovarian (HPO) axis is well recognized to underlie the ovulatory dysfunction of PCOS. While oligo-ovulation is an obvious mechanism, other potential contributors to infertility (such as tubal disease and coexisting male factor) must be additionally screened for in the setting of PCOS-related infertility.

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators (SERMs) represent the prototype of drugs that are of proven efficacy in achieving ovulation induction.

Clomiphene Citrate

Clomiphene citrate (CC) is conventionally considered as the first-line treatment for the management of the normogonadotropic anovulation seen in PCOS.[11,12] A SERM, CC binds to and acts as an estrogen antagonist at the hypothalamo-pituitary estrogen receptors, thus abrogating the estrogen-mediated suppression of pituitary gonadotropins; an increase in the endogenous release of follicle-stimulating hormone (FSH) thus ensues and is responsible for initiating and maintaining ovarian follicle recruitment, growth, and subsequent ovulation. Per conventional protocols, CC is started at doses of 50–150 mg daily for five days (starting on Days 3–7 or 5–9 of the cycle). Recent data suggest that an extended regimen (CC for 10 days) may be efficacious in some patients not responding to the traditional dosing regimen.[13,14] While anecdotally, ovarian response may be seen with doses in excess of 150 mg, an alternative therapy should be considered for patients failing to demonstrate evidence of follicular growth and ovulation with a CC dose in excess of 150 mg/day.

Tamoxifen

Tamoxifen, a sister SERM, may be an option in the subgroup of patients who fail to either ovulate or conceive with CC.[15] Antiestrogenic effects of CC at the level of the endometrium and cervical mucus are suggested as mechanisms that may explain the relatively suboptimal pregnancy rates (30–40 %) seen with CC, despite evidence of an ovulatory response in almost 80 % of the treated population. This may be a concern in patients demonstrating an attenuated endometrial thickness on transvaginal ultrasound despite evidence of ongoing follicular growth and rise in estradiol levels. Due to its favorable effect on the cervical mucus and endometrium, tamoxifen may be considered as an ovulation induction strategy in this group of women. Indeed, ovulation rates of 50–90 % and pregnancy rates of 30–50 % have been reported with tamoxifen, and tamoxifen at doses of 40–80 mg daily on cycle Days 5–9 is regarded as an efficacious alternative in CC-resistant women with PCOS.[15]

Aromatase Inhibitors

The latest addition to the armamentarium of ovulation-inducing agents, aromatase inhibitors (AIs) are increasingly being incorporated into the clinical paradigm for managing ovulatory infertility.[16–19] They act in a manner similar to, and yet are distinct from, SERMs. Inhibition of the enzyme aromatase results in profound reductions in serum and tissue estrogen levels, thus abrogating the estrogen-mediated negative feedback suppression at the hypothalamo-pituitary level; the net result is an increased release of pituitary FSH, which then induces follicular growth. Unlike CC, AIs do not have any adverse effects at the level of the endometrium. Letrozole and anastrozole are the two AIs that have demonstrated success with achieving ovulation induction in CC-resistant patients. Ovulatory response and pregnancy rates associated with AIs are comparable to those seen with CC, but comparative data are sparse. A head-to-head trial comparing the efficacy of CC and AIs in treating ovulatory infertility in women with PCOS is ongoing.[20]

Gonadotropins

In patients who are resistant to, or fail to achieve success with, first- and second-line strategies such as SERMs and AIs, ovarian stimulation through exogenous gonadotropins is of proven efficacy in achieving ovulation and reproductive success, albeit at the risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy.[21] Individualized modifications of treatment protocols—including lower dose step-up, low dose step-down,[22] and minimal stimulation combining CC and low-dose gonadotropin[23]—have demonstrated success in mitigating these treatment-related risks in women with PCOS undergoing infertility treatment with gonadotropins.

Assisted Reproductive Technologies

Recent years have witnessed an expansion in the repertoire of strategies aimed at reducing the risk of OHSS in women undergoing *in vitro* fertilization (IVF); these include a preferential use of

gonadotropin-releasing hormone (GnRH) antagonist for ovulation suppression and the use of GnRH agonist instead of human chorionic gonadotropin to achieve ovulation triggering.[24,25] *In vitro* maturation (IVM),[26] while still regarded an experimental approach, offers a cost-effective strategy with minimal risk of OHSS wherein immature oocytes are recovered and allowed to attain maturity *in vitro* followed by insemination and subsequent embryo transfer.

Laparoscopic Electrocautery of the Ovaries and/or Laparoscopic Ovarian Drilling

For patients with PCOS who have failed to respond to attempts at ovulation induction with first- and second-line strategies such as SERMs and AIs, bilateral electrocautery of the ovarian surface offers a high likelihood of restoring ovulation.[27] Although the underlying mechanisms are yet to be elucidated, a reduction in the hyperandrogenic milieu follows laparoscopic electrocautery of the ovaries (LEO) and/or laparoscopic ovarian drilling (LOD) and is proposed to underlie the resumption of ovarian follicular growth. Spontaneous pregnancy rates within the year following LEO/LOD are comparable to those achieved with gonadotropin use, but without the risk of multiple pregnancies. However, the need for surgery, with its concomitant risks, transient therapeutic efficacy, and the risk of inducing pelvic adhesions, limits the wider use of LEO/LOD in the management of ovulatory infertility in women with PCOS.

Antiandrogens

Given the risk of malformations, such as feminization of a male fetus, linked with antiandrogens, there has to be an imperative need for reliable contraception if these agents are to be prescribed to women of reproductive age who may be at risk of an unplanned pregnancy. Antiandrogen therapy must be discontinued at least three months in advance of attempting conception.

Spironolactone

An aldosterone antagonist recognized for its antihypertensive and potassium-sparing diuretic effects, spironolactone is of proven efficacy against acne, and to a lesser extent against hirsutism related to PCOS.[28-31] Its mechanisms of action include a reduction of adrenal gland testosterone production via depletion of microsomal cytochrome p-450, the competitive inhibition of the androgen receptors in target tissue, and the inhibition of 5-alpha reductase (the enzyme responsible for the conversion of testosterone into the more potent di-hydrotestosterone [DHT]). Improved menstrual cyclicity and resumption of ovulation may be seen in women treated with spironolactone at doses ranging from 50–200 mg/day. Its efficacy against acne is partly mediated through a reduction of sebum production. The main adverse effect is dose-dependent hyperkalemia, which is circumvented by using doses in the recommended range and by regular monitoring of serum potassium level. Periodic evaluation of blood pressure is recommended and symptoms of orthostasis should alert one to the need of lowering the dose. Breast tenderness and fatigue are other mild side effects.

Flutamide

A non-steroidal competitive antagonist of androgen binding to the androgen receptor, flutamide has been studied in the PCOS population and has demonstrated efficacy against acne and hirsutism.[28,30,31]

A risk of serious hepatotoxicity, however, limits its use in the clinical management of PCOS.

Finasteride

A 5-alpha reductase II inhibitor that blocks the conversion of testosterone to its more potent form DHT, finasteride has shown promise in the management of PCOS-related hirsutism.[28,30,31] At doses of 1–5 mg/day, the drug is well tolerated and relatively safe when used to manage symptoms of hyperandrogenism. However, this agent is not currently approved for use in women.

A study that sought to compare objectively spironolactone (100 mg/day), flutamide (250 mg/day), and finasteride (5 mg/day) in the treatment of hirsutism in 40 women found equal clinical efficacy for the three drugs.[30] Others, however, demonstrated spironolactone to be superior to metformin and to finasteride in the treatment of hirsutism in women with PCOS. Others again have shown that the combination of spironolactone and COCs offers synergistic efficacy against hirsutism.[31]

Eflornithine Hydrochloride

Eflornithine hydrochloride is an inhibitor of the enzyme ornithine decarboxylase in human skin. Its topical application has been shown to slow down the growth of hair in treated areas.[32] Adverse events are limited to the application area and include sensations of burning, stinging, and tingling.

Glucocorticoids

Glucocorticoids in low doses may offer cutaneous benefit for those with hyperandrogenemia not responsive to the more commonly used strategies.[33]

Cyproterone Acetate

Cyproterone acetate (CA) is a synthetic steroid that binds to the steroid receptors, exerting progestogenic, antiandrogenic, and weak glucocorticoid-like activity. In combination with ethinyl estradiol in COC formulations (not available in the US),[28,34] this agent has demonstrated efficacy in treating hirsutism in women with PCOS. In COC formulations, CA is used at a 2 mg dose. Although generally well tolerated, it has side effects including weight gain, edema, decreased libido, and headaches.

Treatment Options for Managing Metabolic Abnormalities
Insulin-sensitizing Drugs

Hyperinsulinemia and insulin resistance are recognized as being of pathophysiological relevance for the endocrine and metabolic milieu of PCOS.[3,35-38] They are further recognized to contribute to the hyperandrogenism of PCOS. In turn, the local androgen excess within the ovaries contributes to the ovarian follicular arrest that underlies the polycystic appearance of ovaries, a hallmark of the syndrome. Beyond its causative role in PCOS symptomatology, insulin resistance is central to the processes that underlie the predisposition of women affected by PCOS to long-term comorbidities including type 2 diabetes, CVD, and endometrial pathologies. Given this last fact, insulin-sensitizing strategies (including both pharmacotherapy and lifestyle modifications) are commonly used in the management of PCOS.

Metformin

A safe and well tolerated drug that is of proven efficacy in the management and prevention of type 2 diabetes, metformin is one of the insulin-sensitizing drugs most commonly used in the management of PCOS.[39–42] Its mechanism of action centralizes around a metabolic pathway through decrease in hepatic gluconeogenesis via activation of the AMP-kinase pathway.[41,42] Improved ovulation rates are observed in a variable proportion of women with PCOS treated with metformin. An early meta-analysis that included 13 randomized controlled trials (RCTs) investigating the effect of metformin compared with either placebo or no treatment, or with an ovulation-inducing agent in women with PCOS, demonstrated that metformin alone was effective in achieving ovulation in 46 % of recipients compared with 24 % in the placebo arm.[43] In addition, when metformin was added to CC, 76 % of the recipients in the combination arm achieved ovulation compared with 42 % receiving CC alone (number needed to treat=3.0).

Metformin's efficacy as an ovulation-inducing agent was, however, subsequently refuted in a large RCT that compared the efficacy of metformin or CC alone versus a combination of the two in achieving ovulation, pregnancy, and live birth.[44] Metformin alone emerged as a poor strategy for managing ovulatory infertility compared with CC; however, improved ovulatory and live birth rates were observed in the combination group, suggesting a role for metformin as an adjunct to CC in managing ovulatory disorders of PCOS.

Most recently, in a multicenter, double-blind RCT undertaken in 320 women with PCOS, improved pregnancy and live birth rates were observed after a three-month pre-treatment with metformin (versus placebo) followed by an ovulation-inducing therapy; metformin and placebo were continued until 12 weeks' gestation.[45] Significantly improved pregnancy and live birth rates were observed with metformin pre-treatment compared with placebo in the overall population (pregnancy rate: 53.6 versus 40.4 %, p=0.006; live birth rate: 41.9 versus 28.8 %, p=0.014). Of particular interest were the improved pregnancy and live birth rates seen with metformin pre-treatment compared with placebo in the obese women (pregnancy rate: 49.0 versus 31.4 %, p=0.04; live birth rate: 35.7 versus 21.9 %, p=0.07). Cox proportional regression analysis identified that in women with PCOS, three month pre-treatment with metformin plus standard infertility treatment increased the chance of pregnancy 1.6 times (hazard ratio 1.6, 95 % confidence interval 1.13–2.27) and the authors concluded that this strategy was of particular relevance for the obese women with anovulatory infertility. While the investigators further agreed that the continuation of metformin until the 12th week may have provided a more beneficial milieu for implantation and early fetal growth, the miscarriage rates were comparable in the two treatment arms (15.2 % in the metformin group versus 17.9 % in the placebo arm, p=0.8).

Yet another RCT has recently demonstrated that metformin treatment may reduce the risk of OHSS in women with PCOS undergoing IVF, thus extending the spectrum of comorbidities that may benefit from it.[46]

To summarize, metformin alone holds poor efficacy as an ovulation-inducing agent, although a small percentage of anovulatory women with PCOS are likely to experience improvements in cycle control with the use of metformin. The addition of metformin to ovulation-inducing strategies, however, offers potential benefits in terms of improving treatment-related ovulation and pregnancy rates and reducing the risk of OHSS in women undergoing IVF.

In contrast to its role in the management of PCOS-related infertility, which has come under much scrutiny, a consensus exists regarding the metabolic benefits of metformin in populations at risk of type 2 diabetes. Significant reductions in fasting insulin concentrations and low-density lipoprotein (LDL) cholesterol and improvements in systolic and diastolic blood pressure are described with metformin use in women with PCOS;[42,47,48] a reduction in serum androgens is additionally described, albeit inconsistently.[47,49] However, despite the many metabolic benefits of metformin, the current consensus is that data supporting the treatment of all PCOS patients with metformin are sparse; rather, a comprehensive metabolic evaluation should be undertaken to detect conditions that would benefit from metformin treatment, namely impaired glucose tolerance, impaired fasting glucose, metabolic syndrome, and increased LDL cholesterol.[50]

A recent study compared the efficacy of metformin with lifestyle modification in 40 women with PCOS.[51] After six months of intervention, an improvement of menstrual pattern (by 67 %) and a reduction in body mass index were evident in both groups, whereas a reduction in circulating testosterone levels was observed in the metformin group only. Beyond its potential for direct metabolic benefit, metformin therapy can also facilitate weight loss in some patients, thus maximizing the net metabolic benefit.[51]

In patients with PCOS, metformin is typically prescribed at doses ranging from 500 mg/day to 850 mg three times a day.[52] Higher doses have been shown to be more efficacious in contributing to net weight loss, particularly in the obese and morbidly obese PCOS population.[53] While metformin is a relatively well tolerated therapy, side effects that are commonly seen include gastrointestinal disturbances, such as bloating, gaseousness, loose bowel movements, and a loss in appetite; these gastrointestinal side effects may be ameliorated with the use of extended-release preparations of metformin.[52] Caution is required when considering metformin therapy in patients with renal dysfunction, as lactic acidosis—a life-threatening consequence—has been described with metformin therapy in this setting; reassuringly, abnormal renal function is an unlikely occurrence in the relatively young PCOS population.[52] More recently, concerns have been raised regarding a blunted ovarian response to exogenous gonadotropin therapy in women with PCOS and evidence of borderline ovarian reserve who were being treated with metformin.[54] While the mechanisms were not entirely evident, the authors implied that women with PCOS and compromised ovarian reserve may benefit from discontinuation of metformin therapy prior to the start of controlled ovarian hyperstimulation.

Thiazolidinediones

Thiazolidinediones (TZDs) belong to a family of peroxisome proliferator-activated receptor gamma (PPAR-g) agonists and act primarily by increasing peripheral glucose uptake. The PPAR-g is identified as a transcription factor that regulates adipogenesis as well as being involved in systemic insulin action.[55] The efficacy of TZDs in ameliorating insulin resistance and hyperinsulinemia and in improving

ovarian hyperandrogenism has been observed in women with PCOS.[56–59] Similar to metformin, the effects of TZDs on ovarian function and ovarian follicular development in PCOS have been studied, but with results that are less promising that those obtained with metformin alone.[57,58] A higher ovulation frequency was observed following a six-month treatment using a combination of metformin and a TZD, compared with a TZD alone.[58]

Troglitazone was one of the earliest TZDs introduced in the treatment of PCOS; the drug, however, was withdrawn due to an unacceptable adverse effect profile that included acute liver failure.[60] Safer TZDs have since been introduced. A recent study reports on the effect of pioglitazone, one of the currently approved TZDs, on obesity in women with PCOS; a significant decrease was observed in parameters of central obesity (waist circumference, hip circumference, and waist:height ratio) despite an overall increase in the total body weight and body mass index.[61] The authors postulated that the observed phenomenon reflected the effects of pioglitazone on the subcutaneous fat (proliferation of new adipocytes) and on renal sodium handling (increases sodium and secondary fluid retention). Fat redistribution with a decrease in visceral adiposity is recognized to translate into an improved metabolic profile, suggesting that TZDs may offer a greater metabolic benefit for the overweight and obese compared with metformin.

Although TZD therapy offers some metabolic and endocrine benefits in the PCOS population, significant concerns exist regarding a potential for fetal detriment (fetal loss and growth retardation have been observed in animal studies[62]) as well as potentially serious risks, including myocardial damage, which limits the role of these agents in the clinical management of PCOS. TZDs, however, remain an alternative option for the patient demonstrating a dysmetabolic profile who does not tolerate metformin. The concomitant use of an efficacious birth control strategy is recommended when TZDs are prescribed to women of reproductive age.

Incretins

Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are recently recognized regulators of insulin response and insulin signaling, particularly following meal ingestion. Impaired incretin effect is appreciated in states of insulin resistance including type 2 diabetes; conversely, oral dipeptidyl peptidase-4 (DPP-4) inhibitors and the parenterally administered GLP-1 agonists have demonstrated therapeutic efficacy in improving glycemic control in type 2 diabetics.[63,64] Recent studies have demonstrated lower GIP levels in obese women with PCOS.[65,66] Given that insulin resistance is of pathophysiological relevance to the endocrine and metabolic dysfunction of PCOS, the therapeutic benefit of incretin therapy in this population is plausible.

Dipeptidyl Peptidase-4 Inhibitors

DPP-4 inhibitors (sitagliptin, linagliptin, vildagliptin, and saxagliptin) act by inhibiting the activity of DPP-4, the enzyme that rapidly converts GLP-1 to its inactive state.[67] Studies of sitaglipin therapy in type 2 diabetes have demonstrated efficacious glycemic control when added to either metformin or a TZD—the former having the advantage over TZDs of not causing weight gain.[67,68] Sitagliptin is currently approved as an adjunct to diet and exercise, either as monotherapy or in combination when the

initial agent, such as metformin or pioglitazone, does not provide adequate glycemic control.[64]

GLP-1 Agonists

GLP-1 agonists differ from the oral DPP-4 inhibitors in that they need to be injected.[64,69,70] Commercially available GLP-1 agonists are exenatide and liraglutide, but many additional ones are under development. Exenatide improves glycemic control while reducing body weight and maintaining low rates of hypoglycemia.[69,70] Liraglutide injected once daily has been shown to improve glycemic control in individuals with type 2 diabetes (up to a 1.5 % decrease in glycated hemoglobin) when used as monotherapy or in combination, while simultaneously decreasing weight.[70]

A single study has explored the therapeutic efficacy of exenatide in the PCOS population, with encouraging results.[71] In this 24-week trial undertaken in 60 overweight oligo-ovulatory women with PCOS aged 18–40 years, participants were randomized to one of three treatment groups for 24 weeks: metformin alone at 1,000 mg twice daily, exenatide alone at 10 µg twice daily, or a combination of the two drugs. The primary outcome was menstrual frequency. Secondary outcome measures included changes in ovulation rate, insulin action, anthropometric measures, androgen levels, and inflammatory markers. The drug combination was determined to be superior to the two drugs on their own in improving menstrual cyclicity, ovulation rate, free androgen index, and insulin sensitivity measures as well as in reducing weight and abdominal fat. A significant reduction in weight was observed in both groups given the incretin alone or in combination compared with the group given metformin alone (p=0.003). The authors rightly concluded that larger trials of longer duration are warranted to assess the long-term efficacy and safety of combined metformin and exenatide therapy in overweight women with PCOS.

Acarbose

The therapeutic efficacy of acarbose is attributable to its action on reducing glucose absorption in the gut and thus decreasing post-prandial insulin levels.[72–75] The potential role of acarbose in PCOS has been studied, but its effects on insulin sensitivity parameters, body mass, and vascular function were inconsistent and there was no significant improvement of PCOS-related dyslipidemia.[74,75] Adverse effects, predominantly gastrointestinal, are common, and potentially fatal hepatotoxicity has been reported. Inconsistent efficacy, bothersome side effects, and the risk of liver damage limit the role of this agent in clinical practice.

Inositol Steroisomers

Inositol is a member of the vitamin B complex family; two of its steroisomers, D-chiro-inositol (DCI) and myo-inositol (MYO), have been studied to determine whether they can improve insulin sensitivity and hence whether they are relevant in PCOS management.[76–80] Although earlier data had identified DCI as potentially efficacious, subsequent data failed to confirm its efficacy in PCOS. MYO, however, has shown consistent promise. Improved indices of insulin sensitivity, decrease in serum testosterone, and improved spontaneous ovulation and menstrual cyclicity have been described with the use of MYO in women with PCOS. Additionally, non-statistical improvements in the severity of hirsutism

have been observed following 12-week treatment with MYO. Limited data on the comparative efficacy of MYO and metformin suggest that MYO may be superior in improving ovulatory response and pregnancy rates in women with PCOS. At the recommended doses of 2–4 g per day, MYO is well tolerated with minimal safety concerns, and its incorporation in clinical management paradigms merits consideration.[81]

Lipid-lowering Agents (Statins)

Elevated serum LDL and triglycerides and suppressed high-density lipoprotein levels are commonly encountered in women with PCOS.[1–3,82] Statins inhibit cholesterol biosynthesis, decreasing circulating LDL cholesterol, and offer logical therapeutic benefit for the dislipidemic women who are deemed at an enhanced risk of CVD. The use of statins is associated with a 20 % decrease in cardiovascular mortality per mmol/l of LDL cholesterol reduction achieved.[83] Beyond their lipid-lowering effects, statins are recognized to inhibit ovarian theca-interstitial cell proliferation and ovarian steroidogenesis *in vitro*, thereby holding a potential for ameliorating the hyperandrogenemia of PCOS.[84] Other pleiotropic effects of statins include an anti-inflammatory effect (as reflected in the lowering of serum levels of C-reactive protein [CRP], increased nitric oxide bioavailability, antioxidant properties, and inhibition of inflammatory responses), improved endothelial function, and stabilization of atherosclerotic plaques.[85] Statins may additionally inhibit the effects of insulin and immunoglobulin I on the ovary, and block the oxidative stress-mediated increases in steroidogenesis and insulin resistance.[86]

In a prospective RCT of 113 women with PCOS, simvastatin was found to be superior to metformin alone in decreasing serum testosterone levels.[84] In another double-blind RCT that assigned 20 women with PCOS and LDL>100 mg/dl to atorvastatin (40 mg/day) or placebo for six weeks, atorvastatin was associated with a statistically significant reduction in diastolic blood pressure, total cholesterol, LDL cholesterol, triglycerides, and serum levels of androstenedione and dehydroepiandrosterone sulfate compared with placebo.[85] Interestingly, increased insulin levels were observed in the atorvastatin group, indicating worsening insulin sensitivity despite an improvement in other metabolic parameters; the long-term implications of this finding are unclear. In a head-to-head comparison of two statins (simvastatin and atorvastatin), both agents induced comparable improvement of lipid profile and lowering of CRP level; atorvastatin induced a more significant improvement of insulin resistance, whereas simvastatin was better at lowering testosterone in women with PCOS.[87] Another RCT compared metabolic and endocrine effects of treatment with simvastatin, metformin, and a combination of the two drugs; 113 women with PCOS completed the three-month trial.[88] Simvastatin was deemed superior to metformin alone, and the combination therapy was found to offer no added benefits to those of simvastatin alone.

In a novel study design, the efficacy of short-term statin therapy (eight weeks) for reproductive biology was assessed in 20 women with PCOS undergoing IVF. Statin use was terminated following the triggering of ovulation with human chorionic gonadotropin prior to egg retrieval.[89] The results from this prospective randomized, placebo-controlled trial of 20 mg/day simvastatin showed significant reductions of testosterone, total cholesterol, CRP, and vascular cell

adhesion protein-1 in the simvastatin-treated group compared with controls. Although oocyte maturation, fertility, and clinical pregnancy rates were higher in the statin-treated group compared with placebo, these differences were not of statistical significance, suggesting a need for further clinical trials to clarify the impact of statins on reproductive physiology.[89]

In summary, the use of statins in women with PCOS has been shown to have both metabolic and endocrine benefits; the observed reduction in circulating androgens, however, has not been shown to translate into any improvement in menstrual cyclicity or features of hyperandrogenism. Until further data clarify their facilitatory effects on reproductive performance, and given their potential for teratogenicity, statins should be used with caution and only under approved research protocols in women of reproductive age who seek pregnancy.[90]

Miscellaneous
Opioid Receptor Antagonist

The rationale behind the use of opioid receptor antagonists in PCOS is based on the existing evidence of sympathetic overactivity and elevated β-endorphin release, phenomena that directly influence the release and action of insulin.[91] Naltrexone is an orally administered competitive non-selective opioid receptor antagonist and has been studied in the PCOS population with encouraging, albeit inconsistent results.[92–94] A significant improvement in insulin sensitivity indices has been described with the use of oral naltrexone in hyperinsulinemic women by some, but not all. Gastrointestinal side effects are common and there is a risk of drug interaction with common medications, which limits the use of opioid receptor antagonists in clinical practice.

Orlistat

A gastric and pancreatic lipase inhibitor, orlistat reduces the absorption of dietary fats by inhibiting the hydrolysis of triglycerides.[95,96] Its efficacy in obesity is well established; its use in PCOS has been explored, with evidence of metabolic benefit. Improved parameters of insulin sensitivity and decrease in body mass were evident in PCOS patients following treatment with orlistat combined with dietary modification. At the commonly employed dosing regimen of 120 mg three times a day by mouth during or within an hour of consuming a fat-containing meal, side effects are commonly encountered and include fecal urgency and incontinence, fatty stools or discharge, diarrhea, abdominal discomfort, and flatulence. Possible drug interactions must be considered and ensuing malabsorption may impair the absorption of orally administered medications and fat-soluble vitamins. While orlistat may have a role in the management of PCOS-related obesity, its relevance for managing the endocrinopathy of PCOS is questionable.

Vitamin D

Vitamin D insufficiency has been related to obesity, dyslipidemia, metabolic syndrome, hypertension, and diabetes[97] and accruing data suggest that vitamin D deficiency may be of relevance to the endocrinological and metabolic milieu of PCOS.[97–103] An inverse relationship between circulating levels of 25OHD (a metabolite of vitamin D that reflects an individual's vitamin D status), androgens, and insulin sensitivity is described. Limited data suggest an improvement in insulin sensitivity parameters and menstrual cyclicity following

vitamin D supplementation.[101–103] These findings merit substantiation in appropriately designed RCTs before vitamin D can be added to the list of agents with proven efficacy for the management of PCOS.

Conclusion

As is evident from the summarized literature, a vast array of pharmacotherapies with varying potential benefits is available for the management of PCOS. It is imperative to appreciate that no single agent may address the entire spectrum of concerns (endocrine, metabolic, and clinical) that may present in a woman diagnosed with PCOS given the heterogenous nature of the syndrome. Hormonal strategies such as COCs can efficaciously address menstrual irregularities, offer cutaneous benefits against hyperandrogenic symptoms, and offer endometrial protection against the development of proliferative pathologies, yet it will not mitigate the metabolic abnormalities of PCOS. Similarly, antiandrogen therapy primarily targets cutaneous stigmata of hyperandrogenism and may improve menstrual cyclicity as a secondary outcome; given a possible improvement of ovulatory response with antiandrogen therapy as well as a recognized teratogenic potential, adherence to a reliable contraceptive option is to be stressed when offering antiandrogen therapy to women with PCOS. The safety and efficacy of metformin in offering metabolic benefit in PCOS are well established. Although far less effective than CC as an ovulation-inducing agent, metformin used as an adjunct to ovulation-inducing strategies may improve reproductive outcomes, particularly in obese women with PCOS, and enhance response to treatment in those deemed resistant to CC. TZDs offer little benefit over metformin in the treatment of PCOS-related insulin resistance and are to be avoided in women seeking pregnancy. While metabolic benefits and improvement in PCOS-related hyperandrogenemia are superior with statins than with metformin alone, statins, similarly to TZDs, are to be avoided in women seeking pregnancy. Incretins are a promising class of metabolic modulators and merit further investigation in the PCOS population. The use of MYO is a safe and simple strategy that has shown efficacy against biochemical and clinical endpoints in PCOS management and merits further consideration. ■

1. Azziz R, Woods KS, Reyna R, et al., The prevalence and features of the polycystic ovary syndrome in an unselected population, *J Clin Endocrinol Metab*, 2004;89(6):2745–9.
2. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome, *Fertil Steril*, 2004;81(1):19–25.
3. Goodarzi MO, Dumesic DA, Chazenbalk G, Azziz R, Polycystic ovary syndrome: etiology, pathogenesis and diagnosis, *Nat Rev Endocrinol*, 2011;7(4):219–31.
4. Mu N, Zhu Y, Wang Y, et al., Insulin resistance: A significant risk factor of endometrial cancer, *Gynecol Oncol*, 2012;125(3):751–7.
5. Yildiz BO, Oral contraceptives in polycystic ovary syndrome: risk-benefit assessment, *Semin Reprod Med*, 2008;26(1):111–20.
6. Thorneycroft H, Gollnick H, Schellschmidt I, Superiority of a combined contraceptive containing drospirenone to a triphasic preparation containing norgestimate in acne treatment, *Cutis*, 2004;74(2):123–30.
7. Tan J, Hormonal treatment of acne: review of current best evidence, *J Cutan Med Surg*, 2004;8(Suppl. 4):11–5.
8. Fambrini M, Bargelli G, Peruzzi E, et al., Levonorgestrel-releasing intrauterine system alone as primary treatment in young women with early endometrial cancer: case report, *J Minim Invasive Gynecol*, 2009;16(5):630–3.
9. Luukkainen T, Toivonen J, Levonorgestrel-releasing IUD as a method of contraception with therapeutic properties, *Contraception*, 1995;52(5):269–76.
10. Ahrendt HJ, Adolf D, Buhling KJ, Advantages and challenges of oestrogen-free hormonal contraception, *Curr Med Res Opin*, 2010;26(8):1947–55.
11. Kousta E, White DM, Franks S, Modern use of clomiphene citrate in induction of ovulation, *Hum Reprod Update*, 1997;3(4):359–65.
12. Van Santbrink EJ, Fauser BC, Ovulation induction in normogonadotropic anovulation (PCOS), *Best Pract Res Clin Endocrinol Metab*, 2006;20(2):261–70.
13. Hurst BS, Hickman JM, Matthews ML, et al., Novel clomiphene "stair-step" protocol reduces time to ovulation in women with polycystic ovarian syndrome, *Am J Obstet Gynecol*, 2009;200(5):510e1–4.
14. Badawy A, Allam A, Abulatta M, Extending clomiphene treatment in clomiphene-resistant women with PCOS: a randomized controlled trial, *Reprod Biomed Online*, 2008;16(6):825–9.
15. Dhaliwal LK, Suri V, Gupta KR, Sahdev S, Tamoxifen: An alternative to clomiphene in women with polycystic ovary syndrome, *J Hum Reprod Sci*, 2011;4(2):76–9.
16. Zadehmodares S, Niyakan M, Sharafy SA, et al., Comparison of treatment outcomes of infertile women by clomiphene citrate and letrozole with gonadotropins underwent intrauterine insemination, *Acta Med Iran*, 2012;50(1):18–20.
17. Mitwally MF, Casper RF, Aromatase inhibitors for the treatment of infertility, *Expert Opin Investig Drugs*, 2003;12(3):353–371.
18. Badawy A, Mosbah A, Tharwat A, Eid M, Extended letrozole therapy for ovulation induction in clomiphene-resistant women with polycystic ovary syndrome: a novel protocol, *Fertil Steril*, 2009;92(1):236–9.
19. Misso ML, Wong JL, Teede HJ, et al., Aromatase inhibitors for PCOS: a systematic review and meta-analysis, *Hum Reprod Update*, 2012;18(3):301–12.
20. Legro RS, Kunselman AR, Brzyski RG, et al., The Pregnancy in Polycystic Ovary Syndrome II (PPCOS II) trial: rationale and design of a double-blind randomized trial of clomiphene citrate and letrozole for the treatment of infertility in women with polycystic ovary syndrome, *Contemp Clin Trials*, 2012;33(3):470–81.
21. White DM, Polson DW, Kiddy D, et al., Induction of ovulation with low-dose gonadotropins in polycystic ovary syndrome: an analysis of 109 pregnancies in 225 women, *J Clin Endocrinol Metab*, 1996;81(11):3821–4.
22. Van Santbrink EJ, Donderwinkel FJ, van Dessel HJ, Fauser BC, Gonadotrophin induction of ovulation using a step-down dose regimen: single-center clinical experience in 82 patients, *Hum Reprod*, 1995;10(5):1048–53.
23. Teramoto S, Kato O, Minimal ovarian stimulation with clomiphene citrate: a large-scale retrospective study, *Reprod Biomed Online*, 2007;15(2):134–48.
24. Kol S, Homburg R, Alsbjerg B, Humaidan P, The gonadotropin-releasing hormone antagonist protocol – the protocol of choice for the polycystic ovary syndrome patient undergoing controlled ovarian stimulation, *Acta Obstet Gynecol Scand*, 2012;91(6):643–7.
25. Engmann L, DiLuigi A, Schmidt D, et al., The use of gonadotropin-releasing hormone (GnRH) agonist to induce oocyte maturation after cotreatment with GnRH antagonist in high-risk patients undergoing in vitro fertilization prevents the risk of ovarian hyperstimulation syndrome: a prospective randomized controlled study, *Fertil Steril*, 2008;89(1):84–91.
26. Chian RC, In-vitro maturation of immature oocytes for infertile women with PCOS, *Reprod Biomed Online*, 2004;8(5):547–52.
27. Bayram N, van Wely M, Kaaijk EM, et al., Using an electrocautery strategy or recombinant follicle stimulating hormone to induce ovulation in polycystic ovary syndrome: randomised controlled trial, *BMJ*, 2004;328(7433):192.
28. Koulouri O, Conway GS, A systematic review of commonly used medical treatments for hirsutism in women, *Clin Endocrinol (Oxf)*, 2008;68(5):800–5.
29. Farquhar C, Lee O, Toomath R, Jepson R, Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne, *Cochrane Database Syst Rev*, 2003;(4):CD000194.
30. Moghetti P, Tosi F, Tosti A, et al., Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: a randomized, double blind, placebo-controlled trial, *J Clin Endocrinol Metab*, 2000;85(1):89–94.
31. Paparodis R, Dunaif A, The hirsute woman: challenges in evaluation and management, *Endocr Pract*, 2011;17(5):807–18.
32. Balfour JA, McClellan K, Topical eflornithine, *Am J Clin Dermatol*, 2001;2(3):197–201; discussion 202.
33. Vanky E, Kjøtrød SB, Maesel A, et al., Dexamethasone reduces androgen levels in metformin-treated patients with polycystic ovary syndrome, *Fertil Steril*, 2004;81(2):459–62.
34. Van der Spuy ZM, le Roux PA, Cyproterone acetate for hirsutism, *Cochrane Database Syst Rev*, 2003;(4):CD001125.
35. DeUgarte CM, Bartolucci AA, Azziz R, Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment, *Fertil Steril*, 2005;83(5):1454-60.
36. Dunaif A, Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis, *Endocr Rev*, 1997;18(6):774–800.
37. Azziz R, Carmina E, Dewailly D, et al., Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline, *J Clin Endocrinol Metab*, 2006;91(11):4237–45.
38. Bergh C, Carlsson B, Olsson JH, et al., Regulation of androgen production in cultured human thecal cells by insulin-like growth factor I and insulin, *Fertil Steril*, 1993;59(2):323–31.
39. Diabetes Prevention Program Research Group, Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study, *Diabetes Care*, 2012;35(4):731–7.
40. Diamanti-Kandarakis E, Economou F, Palimeri S, Christakou C, Metformin in polycystic ovary syndrome, *Ann N Y Acad Sci*, 2010;1205:192–8.
41. Moghetti P, Castello R, Negri C, et al., Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation, *J Clin Endocrinol Metab*, 2000;85(1):139–46.
42. Zhou G, Myers R, Li Y, et al., Role of AMP-activated protein kinase in mechanism of metformin action, *J Clin Invest*, 2001;108(8):1167–74.
43. Lord JM, Flight IH, Norman RJ, Metformin in polycystic ovary syndrome: systematic review and meta-analysis, *BMJ*, 2003;327(7421):951–3.
44. Legro RS, Barnhart HX, Schlaff WD, et al., Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome, *N Engl J Med*, 2007;356(6):551–66.
45. Morin-Papunen L, Rantala AS, Unkila-Kallio L, et al., Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial, *J Clin Endocrin Metab*, 2012;97(5):1492–500.
46. Palomba S, Falbo A, Carrillo L, et al., Metformin reduces risk of ovarian hyperstimulation syndrome in patients with polycystic ovary syndrome during gonadotropin-stimulated in vitro fertilization cycles: a randomized, controlled trial, *Fertil Steril*, 2011;96(6):1384–90.e4.
47. Costello M, Shrestha B, Eden J, et al., Insulin-sensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome, *Cochrane Database Syst Rev*, 2007;(1):CD005552.
48. Banaszewska B, Duleba AJ, Spaczynski RZ, Pawelczyk L, Lipids in polycystic ovary syndrome: role of hyperinsulinemia and effects of metformin, *Am J Obstet Gynecol*, 2006;194(5):1266–72.
49. Ortega-González C, Luna S, Hernández L, et al., Responses of serum androgen and insulin resistance to metformin and pioglitazone in obese, insulin-resistant women with polycystic ovary syndrome, *J Clin Endocrinol Metab*, 2005;90(3):1360–5.
50. Marshall JC, Dunaif A, Should all women with PCOS be treated for insulin resistance? *Fertil Steril*, 2012;97(1):18–22.
51. Curi DD, Fonseca AM, Marcondes JA, et al., Metformin versus lifestyle changes in treating women with polycystic ovary syndrome, *Gynecol Endocrinol*, 2012;28(3):182–5.
52. Duleba AJ, Medical management of metabolic dysfunction in PCOS, *Steroids*, 2012;77(4):306–11.
53. Harborne LR, Sattar N, Norman JE, Fleming R, Metformin and

weight loss in obese women with polycystic ovary syndrome: comparison of doses, *J Clin Endocrinol Metab*, 2005;90(8):4593–8.

54. Palomba S, Falbo A, Di Cello A, et al., Does metformin affect the ovarian response to gonadotropins for in vitro fertilization treatment in patients with polycystic ovary syndrome and reduced ovarian reserve? A randomized controlled trial, *Fertil Steril*, 2011;96(5):1128–33.

55. Spiegelman BM, PPAR-gamma: adipogenic regulator and thiazolidinedione receptor, *Diabetes*, 1998;47(4):507–14.

56. Aroda VR, Ciaraldi TP, Burke P, et al., Metabolic and hormonal changes induced by pioglitazone in polycystic ovary syndrome: a randomized, placebo-controlled clinical trial, *J Clin Endocrinol Metab*, 200;94(2):469–476.

57. Rautio K, Tapanainen JS, Ruokonen A, Morin-Papunen LC, Endocrine and metabolic effects of rosiglitazone in overweight women with PCOS: a randomized placebo-controlled study, *Human Reproduction*, 2006;21(6):1400–7.

58. Baillargeon JP, Jakubowicz DJ, Iuorno M, et al., Effects of metformin and rosiglitazone, alone and in combination, in nonobese women with polycystic ovary syndrome and normal indices of insulin sensitivity, *Fertil Steril*, 2004;82(4):893–902.

59. Dunaif A, Scott D, Finegood D, et al., The insulin-sensitizing agent troglitazone improves metabolic and reproductive abnormalities in the polycystic ovary syndrome, *J Clin Endocrinol Metab*, 1996;81(9):3299–306.

60. Neuschwander-Tetri BA, Isley WL, Oki JC, et al., Troglitazone-induced hepatic failure leading to liver transplantation. A case report, *Ann Intern Med*, 1998;129(1):38–41.

61. Asadipooya K, Kalantar-Hormozi M, Nabipour I, Pioglitazone reduces central obesity in polycystic ovary syndrome women, *Gynecol Endocrinol*, 2012;28(1):16–19.

62. Glintborg D, Andersen M, Thiazolinedione treatment in PCOS – an update, *Gynecol Endocrinol*, 2010;26(11):791–803.

63. Cefalu WT, Evolving treatment strategies for the management of type 2 diabetes, *Am J Med Sci*, 2012;343(1):21–6.

64. Cefalu WT, The physiologic role of incretin hormones: clinical applications, *J Am Osteopath Assoc*, 2010;110(3 Suppl. 2):S8–14.

65. Pontikis C, Yavropoulou MP, Toulis KA, et al., The incretin effect and secretion in obese and lean women with polycystic ovary syndrome: a pilot study, *J Womens Health (Larchmt)*, 2011;20(6):971–6.

66. Vrbikova J, Hill M, Bendlova B, et al., Incretin levels in polycystic ovary syndrome, *Eur J Endocrinol*, 2008;159(2):121–7.

67. Nauck MA, Meininger G, Sheng D, et al., Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial, *Diabetes Obes Metab*, 2007;9(2):194–205.

68. Olansky L, Reasner C, Seck TL, et al., A treatment strategy implementing combination therapy with sitagliptin and metformin results in superior glycaemic control versus metformin monotherapy due to a low rate of addition of antihyperglycaemic agents, *Diabetes Obes Metab*, 2011;13(9):841–9.

69. Garber AJ, Long-acting glucagon-like peptide 1 receptor agonists: a review of their efficacy and tolerability, *Diabetes Care*, 2011;34(Suppl. 2):S279–84.

70. Derosa G, Maffioli P, Glp-1 agonists exenatide and liraglutide:

a review about their safety and efficacy, *Curr Clin Pharmacol*, 2012 Mar 20 [Epub ahead of print].

71. Elkind-Hirsch K, Marrioneaux O, Bhushan M, et al., Comparison of single and combined treatment with exenatide and metformin on menstrual cyclicity in overweight women with polycystic ovary syndrome, *J Clin Endocrinol Metab*, 2008;93(7):2670–8.

72. Ciotta L, Calogero AE, Farina M, et al., Clinical, endocrine and metabolic effects of acarbose, an alpha-glucosidase inhibitor, in PCOS patients with increased insulin response and normal glucose tolerance, *Hum Reprod*, 2001;16(10):2066–72.

73. Tugrul S, Kutlu T, Pekin O, et al., Clinical, endocrine, and metabolic effects of acarbose, a alpha-glucosidase inhibitor, in overweight and nonoverweight patients with polycystic ovarian syndrome, *Fertil Steril*, 2008;90(4):1144–8.

74. Penna IA, Canella PRB, Reis RM, et al., Acarbose in obese patients with polycystic ovarian syndrome: a double-blind, randomized, placebo-controlled study, *Hum Reprod*, 2005;20(9):2396–401.

75. Araujo Penna I, Canella PR, Vieira CS, et al., Cardiovascular risk factors are reduced with a low dose of acarbose in obese patients with polycystic ovary syndrome, *Fertil Steril*, 2007;88(2):519–22.

76. Nestler JE, Jakubowicz DJ, Reamer P, et al., Ovulatory and metabolic effects of D-chiro-inositol in the polycystic ovary syndrome, *N Engl J Med*, 1999;340(17):1314–20.

77. Unfer V, Carlomagno G, Effects of myo-inositol in women with PCOS: a systematic review of randomized controlled trials, *Gynecol Endocrinol*, 2012;28(7):509–15.

78. Papaleo E, Unfer V, Baillargeon JP, et al., Myo-inositol in patients with polycystic ovary syndrome: a novel method for ovulation induction, *Gynecol Endocrinol*, 2007;23(12):700–3.

79. Costantino D, Minozzi G, Minozzi E, Guaraldi C, Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial, *Eur Rev Med Pharmacol Sci*, 2009;13(2):105–10.

80. Gerli S, Papaleo E, Ferrari A, Di Renzo GC, Randomized, double blind placebo-controlled trial: effects of myo-inositol on ovarian function and metabolic factors in women with PCOS, *Eur Rev Med Pharmacol Sci*, 2007;11(5):347–54.

81. Carlomagno G, Unfer V, Inositol safety: clinical evidences, *Eur Rev Med Pharmacol Sci*, 2011;15(8):931–6.

82. Legro RS, Kunselman AR, Dunaif A, Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome, *Am J Med*, 2001;111(8):607–13.

83. Rutishauser J, Statins in clinical medicine, *Swiss Med Wkly*, 2011;141:w13310.

84. Izquierdo D, Foyouzi N, Kwintkiewicz J, Duleba AJ, Mevastatin inhibits ovarian theca-interstitial cell proliferation and steroidogenesis, *Fertil Steril*, 2004;82(Suppl. 3):1193–7.

85. Raja-Khan N, Kunselman AR, Hogeman CS, Effects of atorvastatin on vascular function, inflammation, and androgens in women with polycystic ovary syndrome: a double-blind, randomized, placebo-controlled trial, *Fertil Steril*, 2011;95(5):1849–52.

86. Kodaman PH, Duleba AJ, HMG-CoA reductase inhibitors: do they have potential in the treatment of polycystic ovary syndrome?, *Drugs*, 2008;68(13):1771–85.

87. Kaya C, Pabuccu R, Cengiz SD, Dünder I, Comparison of the effects of atorvastatin and simvastatin in women with polycystic ovary syndrome: A prospective, randomized study, *Exp Clin Endocrinol Diabetes*, 2010;118(3):161–6.

88. Banaszewska B, Pawelczyk L, Spaczynski RZ, Duleba AJ, Comparison of simvastatin and metformin in treatment of polycystic ovary syndrome: prospective randomized trial, *J Clin Endocrinol Metab*, 2009;94(12):4938–45.

89. Rashidi B, Abediasl J, Tehraninejad E, Simvastatin effects on androgens, inflammatory mediators, and endogenous pituitary gonadotropins among patients with PCOS undergoing IVF: results from a prospective, randomized, placebo-controlled clinical trial, *J Investig Med*, 2011;59(6):912–6.

90. Taguchi N, Rubin ET, Hosokawa A, et al., Prenatal exposure to HMG-CoA reductase inhibitors: effects on fetal and neonatal outcomes, *Reprod Toxicol*, 2008;26(2):175–7.

91. Sverrisdóttir YB, Mogren T, Kataoka J, et al., Is polycystic ovary syndrome associated with high sympathetic nerve activity and size at birth? *Am J Physiol Endocrinol Metab*, 2008;294(3):E576–81.

92. Guido M, Romualdi D, Lanzone A, Role of opioid antagonists in the treatment of women with glucoregulation abnormalities, *Curr Pharm Des*, 2006;12(8):1001–12.

93. Fruzzetti F, Bersi C, Parrini D, et al., Effect of long-term naltrexone treatment on endocrine profile, clinical features, and insulin sensitivity in obese women with polycystic ovary syndrome, *Fertil Steril*, 2002;77(5):936–44.

94. Hadziomerovic-Pekic D, Wildt L, Weiss JM, et al., Metformin, naltrexone, or the combination of prednisolone and antiandrogenic oral contraceptives as first-line therapy in hyperinsulinemic women with polycystic ovary syndrome, *Fertil Steril*, 2010;94(6):2385–8.

95. Panidis D, Farmakiotis D, Rousso D, et al., Obesity, weight loss, and the polycystic ovary syndrome: effect of treatment with diet and orlistat for 24 weeks on insulin resistance and androgen levels, *Fertil Steril*, 2008;89(4):899–906.

96. Jayagopal V, Kilpatrick ES, Holding S, et al., Orlistat is as beneficial as metformin in the treatment of polycystic ovarian syndrome, *J Clin Endocrinol Metab*, 2005;90:729–33.

97. Holick MF, Vitamin D deficiency, *N Engl J Med*, 2007;357(3):266–81.

98. Thys-Jacobs S, Donovan D, Papadopoulos A, et al., Vitamin D and calcium dysregulation in the polycystic ovarian syndrome, *Steroids*, 1999;64(6):430–5.

99. Hahn S, Haselhorst U, Tan S, et al., Low serum 25-hydroxyvitamin D concentrations are associated with insulin resistance and obesity in women with polycystic ovary syndrome, *Exp Clin Endocrinol Diabetes*, 2006;114(10):577–83.

100. Wehr E, Pilz S, Schweighofer N, et al., Association of hypovitaminosis D with metabolic disturbances in polycystic ovary syndrome, *Eur J Endocrinol*, 2009;161(4):575–82.

101. Selimoglu H, Duran C, Kiyici S, et al., The effect of vitamin D replacement therapy on insulin resistance and androgen levels in women with polycystic ovary syndrome, *J Endocrinol Invest*, 2010;33(4):234–8.

102. Kotsa K, Yavropoulou MP, Anastasiou O, Yovos JG, Role of vitamin D treatment in glucose metabolism in polycystic ovary syndrome, *Fertil Steril*, 2009;92(3):1053–8.

103. Rashidi B, Haghollahi F, Shariat M, Zayerii F, The effects of calcium-vitamin D and metformin on polycystic ovary syndrome: a pilot study, *Taiwan J Obstet Gynecol*, 2009;48(2):142–7.