

Treatment of polycystic ovary syndrome: recent trial results

Polycystic ovary syndrome, the most common endocrinopathy affecting women of reproductive age, is considered a form of metabolic syndrome stemming from the interaction of environment and genetic susceptibility. Accordingly, diet modification and a structured exercise protocol are the preferred approaches in the management of this condition. Pharmacological treatment options are moderately effective and, there are plenty of available therapies, such as contraceptive pills, insulin sensitizers and antiandrogens, amongst others. Drugs can be prescribed dependent on the status of the patient (e.g., during pregnancy or adolescence) and the desired outcome (e.g., treatment of hirsutism, irregular menses, infertility). Various drug combinations have been proposed and tested (e.g., spironolactone and metformin), and have demonstrated superior efficacy in trials. In this review, we present the data from trials in polycystic ovary syndrome management and assess the relative benefits of currently available treatments.

Keywords: clinical trials • clomiphene citrate • hormonal contraception • metformin • polycystic ovary syndrome • spironolactone

Polycystic ovary syndrome (PCOS) is characterized by irregular menstrual cycles, chronic an-ovulation and hyperandrogenism in addition to many metabolic manifestations such as obesity, hyperlipidemia, hyperinsulinemia, insulin resistance, dysglycemia, increased risk of cardiovascular disease (CVD) and probably some cancers (endometrial, ovarian and breast cancer) [1]. In 1935, Stein and Leventhal [2] described masculinized women with amenorrhea, sterility and enlarged ovaries containing multiple cysts. Prevalence of PCOS is 5–10% among women of reproductive age.

PCOS is now recognized as a metabolic as well as reproductive disorder associated with increased risk for Type 2 diabetes. Affected women have marked insulin resistance, independent of obesity. There is a post-binding defect in receptor signaling likely due to increased receptor and insulin receptor substrate-1 serine phosphorylation that selectively affects metabolic but not mitogenic pathways in classic insulin target tissues and in the ovary. Constitutive activation of serine kinases in the MAPK-ERK pathway may contribute to resistance to insulin's metabolic actions in skeletal muscle. Insulin functions as a co-gonadotropin through its cognate receptor to modulate ovarian steroidogenesis. Genetic disruption of insulin signaling in the brain has indicated that this pathway is important for ovulation and body weight regulation. Hyperandrogenemia also contributes to insulin resistance in PCOS [3]. The treatment goals in PCOS are:

- Address hyperandrogenic symptoms (hirsutism, acne, androgenic alopecia);
- Address associated metabolic abnormalities so as to reduce risk of Type 2 diabetes and CVD;
- Regularize cycles in oligomenorrhea and induce ovulation for those desiring pregnancy.

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This paper will focus on the outcomes of recent large well-designed trials and meta-analyses conducted to research methods for management of PCOS with above-mentioned outcomes in mind.

Lifestyle modification: diet & exercise

Lifestyle modification including diet control and exercise is one of the mainstay interventions in treatment of PCOS because weight loss can restore the ovulatory cycles as well as improve insulin sensitivity. Weight loss has been shown to be beneficial for both metabolic and reproductive dysfunction in obese women with PCOS. As little as 5-10% reduction in body weight improves menstrual irregularities [4]. The major outcome of lifestyle modifications is weight loss and it is this alteration in body phenotype that is desirable as the first line management especially among overweight or obese women with PCOS. Various modalities in practice to achieve weight loss are regular aerobic exercise 30 min daily or 150 min per week and low caloric and high fiber diet. Sometimes medications for weight loss or bariatric surgery [5-7] can be tried. In a recent Cochrane review by Moran et al. [8] the authors showed that lifestyle intervention improves body composition, hyperandrogenism and insulin resistance in women with PCOS.

In a recent study by Domecq et al. [9] in 2013 a systematic meta-analysis was done of randomized controlled trials that enrolled woman of any age with PCOS who received lifestyle modification and compared them against women who received no intervention, minimal intervention or metformin (MET). Nine trials were included enrolling 583 women with a high loss to follow-up rate, lack of blinding and short follow-up. Compared with minimal intervention, lifestyle modification significantly reduced fasting blood glucose (weighted mean difference, -2.3 mg/dl, 95% CI, -4.5 to -0.1, p = 0.04) and fasting blood insulin (weighted mean difference, -2.1 µU/ml, 95% CI, -3.3 to -1.0, p < 0.001). Changes in body mass index (BMI) were associated with changes in fasting blood glucose (p < 0.001). MET was not significantly better than lifestyle modification in improving blood glucose or insulin levels. No significant effect of lifestyle modification on pregnancy rate was found, and the effect on hirsutism was unclear.

Hoeger *et al.* [10] carried out a randomized placebocontrolled trial for 48 weeks of intensive lifestyle modification and/or MET therapy in 38 overweight or obese women with PCOS. The subjects were randomized to one of four arms: MET 850 mg twice a day, lifestyle modification plus MET 850 mg twice a day, lifestyle modification plus placebo or placebo alone. There was 39% dropout majority occurring within 24 weeks. Most significant weight reduction occurred in lifestyle modification plus MET arm. Though significant androgen reduction occurred in combination arm but ovulation rates did not differ between two groups. There is not much data regarding effect of lifestyle modifications on fertility and pregnancy outcomes and further studies are required in this regard.

Wild et al. [11] assessed cardiovascular risks in PCOS women and recommended measures for prevention of CVD. Obese PCOS subjects, cigarette smoker, those with dyslipidemia, hypertension, impaired glucose tolerance (IGT) and subclinical vascular disease are all at risk of coronary artery disease, increased carotid artery intima media thickness, increased coronary artery calcification, fatal/nonfatal cardiovascular events. Those with metabolic syndrome and/or Type 2 diabetes mellitus and overt vascular or renal disease are also at high risk for CVD. BMI, waist circumference, serum glucose, lipid profile and blood pressure determinations were recommended in all PCOS subjects in this study. Oral glucose tolerance test (OGTT) is recommended in those with obesity, advanced age, family history of diabetes or previous history of gestational diabetes. The authors recommended lifestyle management for primary CVD prevention, targeting low-density and high-density lipoprotein (LDL and HDL) cholesterol and adding insulin-sensitizing and other drugs if dyslipidemia or other risk factors persist.

Diamanti-Kandarakis et al. [12] in their study showed that dietary advanced glycation end products (AGE) plays an important role in the pathophysiology of PCOS. Twenty-three women with PCOS (mean ± SD, age: 23.4 ± 5.7 years; BMI: 26 ± 5.7 kg/m²) underwent the following 2-month dietary regimens: a hypocaloric diet with ad-libitum AGEs content (Hypo), anisocaloric diet with high AGEs (HA) and an isocaloric diet with low AGEs (LA). Metabolic, hormonal and oxidative stress status was assessed and AGE levels were determined in all subjects after the completion of each dietary intervention. Serum levels of AGEs, testosterone, oxidative stress, insulin and HOMA-IR index were significantly increased on the HA compared with the Hypo diet and subsequently decreased on the LA diet (compared with HA: p < 0.05 for all parameters). BMI remained unaltered throughout the HA and LA periods compared with the Hypo period. Serum AGEs were strongly correlated with insulin, as well as with HOMA, during the LA dietary period (r = 0.53, p = 0.02 and r = 0.51, p = 0.03, respectively). For the same period, dietary AGEs were correlated with insulin levels (rho = 0.49, p = 0.04). So the authors concluded that change in dietary AGEs in women with PCOS also leads to change in metabolic, stress and oxidative biomarkers. Thus a diet low in AGEs along

with lifestyle modification is recommended in women with PCOS.

Hormonal contraception

In the chronic treatment of PCOS, oral contraceptive pills (OCPs) are commonly used to induce regular menses, protect the endometrium and ameliorate androgenic symptoms. OCPs are estrogen and progestin containing preparations and are popular first line medications in women who do not want pregnancy. Though having androgenic activity, progestin component of OCPs suppresses LH levels and thus ovarian androgen production while an estrogen component increases sex hormone binding globulin levels which help to reduce bioavailable androgen levels. OCPs now generally contain progestins such as norgestimate, desogestrel, drospirenone, dienogest and chlormadinon acetate which are less androgenic compared with previous ones (e.g., levonorgestrel, gestodene and so on). Progestins such as drospirenone, cyproterone acetate also have antiandrogenic properties due to their antagonizing effects on the androgen receptor and/or to the inhibition of 5α -reductase activity [13]. The Endocrine Society [14] recommends OCPs (i.e., oral contraceptives, patches and vaginal rings and so on) as first line management for menstrual abnormalities, hirsutism, acne, etc., in women with PCOS. There is some suggestion from the literature that "extended-cycle OCPs (vs cyclic therapy) offer greater hormonal suppression and prevent rebound ovarian function during the pill-free interval" [15].

Cross-sectional studies in healthy women have revealed decreased insulin sensitivity and increased glucose response to a glucose load during OCPs use, although these results varied according to the estrogen dose and the type of progestin used [16]. Estrogens impair carbohydrate tolerance, dose-dependently, as do androgens and progestins of greater androgenicity. Studies have also shown that hormonal contraception had deleterious effect on glucose metabolism in obese women with PCOS [17-19]. Long-term effect of OCPs on glucose tolerance in women with PCOS remains unclear. A Cochrane meta-analysis concluded that OCPs do not have a significant effect on glucose tolerance, although this conclusion was based on limited and low-quality evidence [20] and hence further studies are required to confirm the findings (Table 2). Mastorakos et al. [21] compared the effects of combined oral contraceptives containing cyproterone acetate or desogestrel on insulin sensitivity in 36 adolescent PCOS subjects in a prospective randomized clinical trial. They found that after 12 months of treatment homeostasis model assessment of insulin resistance (HOMA-IR) increased significantly in both groups. Those subjects who were on cyproterone acetate-containing OCPs had more insulin secretion and hyperinsulinemia as has been described by Diamanti-Kandarakis et al. [22]. Nader et al. [23] tried to explain the diverse effects of OCPs on carbohydrate metabolism through a common hypothesis. According to their research the effect of OCPs on carbohydrate metabolism is determined by "the degree of androgenicity of the woman and the androgen-lowering effect of the pill, genetically determined endogenous insulin sensitivity, anthropometric differences that can affect insulin action and (iv.) the natural history of PCOS or environmental influences such as puberty, which is associated with decreased insulin sensitivity". Complex interplay of all these factors determines the effect of OCPs on glucose metabolism and insulin sensitivity (Table 1).

Diamanti-Kandarakis et al. [24] compared the effects of oral contraceptives and MET on atherogenic markers, including serum levels of AGEs and C-reactive protein (CRP), in lean women (BMI below 25 kg/m²) with PCOS, defined by NIH criteria. In a prospective open-label study, 120 women with PCOS were treated for 6 months with one of the following treatments: ethinylestradiol plus cyproterone acetate (OCPs1, n = 40) or ethinylestradiol plus drospirenone (OCPs2, n = 40) or MET (n = 40). The three groups were age and BMI matched. At 6 months serum AGEs were decreased in group OCPs1 (p = 0.005) and group MET (p = 0.001), whereas these were marginally decreased in group OCPs2 (p = 0.069). Treatment with MET was associated with a greater percent decrease of AGEs. CRP was decreased with MET (p < 0.001), but was increased with OCPs (p < 0.001). Thus the authors concluded that MET is superior to OCPs in reducing serum AGE and CRP in lean PCOS patients.

In general, regarding the effect on lipid metabolism, OCPs reduce LDL and total cholesterol and elevate HDL and triglycerides. However, the effect on the lipid metabolism depends on the formulation of OCPs used. Higher triglyceride concentrations are seen with less androgenic progestins when estrogenic activity prevails, there is an increase in HDL-cholesterol and a decrease in LDL-cholesterol levels, whereas the opposite occurs when androgenic activity is higher [25,26]. Increased TG, often together with increased total cholesterol levels, appears to be the commonest adverse effect of OCP treatment in women with PCOS. The potential effect of OCPs on TG levels is thought to be due to the effect of the estrogen component in the liver and resulting in reduction of triglyceride clearance. Thus, OCPs may have a negative effect on the metabolic aberrations of women with PCOS and the long-term benefits are unclear, especially in those with IGT, T2DM and Dyslipidemia [27].

Clinical Trial Outcomes Ganie, Chakraborty & Rehman

lable 1. Summary	of the studies l	ngnig	nting the effect of	of oral contraceptive pills o	on lipid metabolism	and insulin sensit	ivity.		
Study (year)	Subjects (N)	BMI	Design	Intervention/subgroups	Insulin sensitivity	Total cholesterol	HDL cholesterol	TG Re	jf.
Korytkowski <i>et al.</i> (1995)	19	28	CT (PCOS vs Control)	PCOS	\rightarrow	¢	¢	÷	[69]
				Controls	\rightarrow	¢	¢	←	
Dahlgren <i>et al.</i> (1998)	28	<28	CT (OCPs vs GnRH analog	Combined oral contraceptives	\rightarrow	¢	ND	←	[0]
				GnRH analogues	÷	¢	ND	¢	
Armstrong <i>et al.</i> (2001)	11	<28	Observational	PCOS	¢	ND	ND	DN	[1]
Cibula <i>et al.</i> (2002)	22	<30	CT (PCOS vs Control)	PCOS	¢	ND	ND	DN	[2]
				Controls	¢	ND	ND	ND	
Vrbikova <i>et al.</i> (2004)	24	<30	RCT	Combined oral contraceptives	\rightarrow	~	÷	←	[3]
				TTSE-CPA	¢	€	¢	¢	
Guido <i>et al.</i> (2004)	18	<25	Observational	Drosiperinone	\$	Ť	¢	↓	[4]
BMI: Body mass index CP/ sydrome; RCT: Randomize Adapted with permission ⁻	A: Cyproterone aceta ed control trial; TG: TI from [13] © Oxford L	ite; CT: Cli riglycerid€ Jniversity	inical trial; GnRH: Gona ss; TTSE: Transdermal es Press (2005).	udotropin releasing hormone; HDL: H strogen; Vs: Versus; ↔: no significant	ligh density lipoprotein; ND t change; J1: significant cha	Not done; OCP: Oral c nge.	ontraceptive pill; PCOS: P	olycystic ovary	

Table 2. Therapeutic options in	polycystic ovary syndrome.
Problem	Therapy
Hirsutism	Antiandrogens (e.g., spironolactone and finasteride) combined contraceptive (ethinyl estradiol plus cyproterone acetate)
Infertility	Clomiphene citrate gonadotropins assisted reproductive techniques (e.g., <i>in vitro</i> fertilization)
Type 2 diabetes	Metformin thiazolidinediones
Impaired glucose tolerance	Lifestyle modification metformin
Obesity	Lifestyle modification bariatric surgery

Besides the above concerns, there is a possibility of increased risk of venous thromoembolism in combined hormonal contraceptive users and it is dependent on the dose of estrogen and independent of the progestogen component. There are insufficient data about whether women with PCOS face increased risk of thromoembolism with OCPs and therefore, further studies are required. In fact there is no consensus or any guidelines regarding optimal duration of treatment with OCPs in women with PCOS. OCPs being drugs of choice in the USA are not as popular in other countries owing to many factors including social prohibitions in adolescent PCOS patients.

Insulin sensitizers

Metformin

Metformin (MET), a biguanide, has long been used as oral hypoglycemic agent in the treatment of Type 2 diabetes. MET was approved by US FDA in 1994 in the United States. MET exerts its principal metabolic action and especially its glucoregulatory action upon the liver. In liver MET causes AMPKinase activation and also causes activation of insulin signaling and subsequently inhibition of lipogenic enzymes acetylcoA carboxylase and inhibition of gluconeogenic enzymes like hexokinase, pyruvate kinase. This finally leads to decreased lipogenesis and gluconeogenesis and increased fatty acid oxidation, glucose uptake and glycosis. In skeletal muscle also it causes decreased lipogenesis and increased fatty acid oxidation by same mechanisms. AMP kinase activation in muscle causes activation of protein kinase C and GLUT4 and there is activation of insulin signaling that increases basal as well as insulin-dependent glucose uptake respectively thus decreasing insulin resistance. MET affects ovarian function in two ways, through the alleviation of insulin excess acting upon the ovary and through direct ovarian effects [28]. Decreased CYP17 activity has been found in theca cells in PCOS women treated with MET either by direct effect or due to lowering of insulin levels and subsequent suppression of insulin-induced PI3K activity. By reducing insulin levels, MET may inhibit LH receptor expression as well as StAR, HSD3β and CYP11A1 activity in granulosa cells. "MET-induced AMPK activation may not only decrease StAR, HSD3β and CYP11A1 activity in granulosa cells, but also enhance antioxidant defences at the ovarian tissue level. These mechanisms may contribute to the inhibition of sex steroid overproduction and of premature luteinization (due to premature LH receptor expression), and consequently attenuate androgen excess and improve ovulation". Since AMPK subunits are abundantly expressed in rat ovary (oocyte, corpus luteum, granulosa and theca cells) [29], AMPK may contribute to several ovarian processes and mediate MET's action on the ovary (Figure 1).

MET in PCOS was first used in 1994 in a small study conducted at the University of the Andes [30] on 26 women with PCOS who were given MET 1.5 g/day for 8 weeks. There was significant reduction in waist– hip ratio, systolic blood pressure from baseline post MET therapy. There was also a sharp reduction in testosterone, androstenedione and dehydroepiandrosterone levels. Since then there has been a multitude of publications on use of MET in women with PCOS suggesting both metabolic and reproductive benefits like improvement in ovulation, reduction in serum androgen levels.

Advanced glycation end products (AGE) that is atherogenic has been found to be raised in plasma of PCOS women. In a recent study by Diamanti-Kandarakis *et al.* [31], the effect of MET on plasma AGE levels was investigated. Twenty-two PCOS women and 22 normal women were taken. PCOS women were given MET 1700 mg daily for 6 months. AGE levels were reduced after MET administration in 22 women with PCOS (9.98 \pm 0.13 [before MET] vs 9.86 \pm 0.11 [after MET], p = 0.05). There was also a significant drop in testosterone levels and free androgen index after MET therapy but BMI was unchanged.

In a recent Cochrane review Tang *et al.* reviewed randomized controlled trials of insulin sensitizing drugs like MET, rosiglitazone, pioglitazone and D-chiro-inositol compared with placebo, no treatment or in combination with ovulation induction agent like clomiphene. They analysed 44 trials (comprising



Figure 1. Mechanism of action of metformin in polycystic ovary syndrome. Data taken from [28]. © European Society of Endocrinology (2010).

3992 women), 38 of them used MET involving 3495 women [32]. Clinical pregnancy rates improved with MET versus placebo (pooled OR 2.31, 95% CI 1.52–3.51, eight trials, 707 women) and combination of MET and clomiphene versus clomiphene alone (pooled OR 1.51, 95% CI 1.17–1.96, 11 trials, 1208 women). But MET did not improve live birth rate when used alone or combination with clomiphene. Obese women who took clomiphene also had improved live birth rate and clinical pregnancy rate compared with MET alone. So they concluded that the use of MET for improving reproductive outcome in PCOS women is limited.

In a Cochrane review published in 2007, Costello *et al.* [33] compared efficacy and safety of insulin sensitizing drugs versus OCPs in long-term treatment of PCOS. In this meta-ana-lysis six trials were included – four compared MET versus OCPs (n = 104) and two compared OCPs combined with MET versus OCPs alone (n = 70). Results suggested no difference in effect on hirsutism and acne between MET and OCPs. No definite benefit of MET for preventing diabetes, CVD was found because of insufficient data. MET was less effective than the OCPs in improving menstrual pattern (OR = 0.08, 95% CI 0.01–0.45). MET was also found to be less effective in reducing serum testosterone levels. Fasting insulin levels were lower in MET group but no evidence was found that fasting glucose was also reduced. Thus it was found that OCPs improved menstrual pattern and serum androgens better while improvement in fasting insulin and triglyceride levels occurs with MET.

Misso et al. showed in their systematic review that both clomiphene citrate and MET are better than placebo for increasing ovulation and pregnancy rates, but clomiphene is more effective than MET for ovulation, pregnancy and live birth rates, in PCOS patients with BMI >30 kg/m² [34]. Combination of the two drugs was superior to either drug alone. In a recent metaanalysis Misso et al. further compared the effectiveness of MET and clomiphene citrate for improving fertility outcomes in women with PCOS and BMI <32 kg/m² as studied in randomized trials of the drugs till 2011. The authors concluded from four major randomized control trials (RCTs) that there was no difference between the two drugs in terms of ovulation, pregnancy, live birth, miscarriage and multiple pregnancy rates in nonobese PCOS patients [35].

In a recent study, Morin-Papunen *et al.* [36] studied MET as a treatment of infertility in PCOS. In this multicenter, randomized (1:1), double-blind, placebocontrolled study 320 women with PCOS and anovulatory infertility were randomized to MET (n = 160, obese women, 1000 mg two times daily; nonobese

subjects, 500 mg + 1000 mg daily) or identical doses of placebo (n = 160). At 3 months follow-up another appropriate infertility treatment was combined if necessary. In case of pregnancy MET/placebo was continued up to the 12th week. It was determined that miscarriage rates were low and similar in the two groups (MET 15.2% vs placebo 17.9%, p = 0.8). Intent-totreat analysis showed that MET significantly improved pregnancy rate and live birth rate versus placebo in the whole study population. It was therefore concluded that obese anovulatory infertile women benefitted from 3 month pre-treatment with MET before routine ovulation induction. Diamanti-Kandarakis et al. [37] recently analysed the above trial. According to the author the study had the following strengths - multicentre trial design, double-blind placebo-controlled randomized study protocol, fairly large dataset with well-defined and well-matched subgroups of patients and the use of intention-to-treat analysis and measurement of clinically relevant outcomes like pregnancy rate and live birth rate. Limitations of the study were incomplete data on post-treatment BMI of study subjects, and the inclusion of weight loss as time-dependent covariate in the intention-to-treat analysis which might have confounded the results. The study did not, it was concluded, allow for a clear evaluation of the potential effect of MET on body weight, because the investigators do not provide data on the BMI and metabolic parameters of patients at the end of the study. Over 50% patients in both placebo and MET groups were not hyperandrogenic which can contribute to heterogeneity in fertility related aspects as well as affecting response to treatment. Morin-Papunen et al. state that the study participants had experienced anovulatory infertility for at least 6 months, whereas the established medical definition of infertility is the failure to conceive following 12 months of unprotected intercourse. So the women enrolled before they qualified as medically infertile may have naturally conceived during the study period. Another important aspect addressed in the study by Morin-Papunen et al. was continuation of MET till first 12 weeks of pregnancy. The concept that MET therapy during pregnancy may improve the intrauterine milieu for implantation and early fetal development awaits confirmation by future randomized controlled studies

Diamanti-Kandarakis *et al.* studied the beneficial effects of MET on indices of low grade chronic inflammation in PCOS women [38]. The objective of the study was to investigate whether soluble inflammatory markers (soluble intercellular adhesion molecule-1 [sICAM-1], soluble endothelial leukocyte adhesion molecule-1 [sE-selectin], soluble vascular cell adhesion molecule-1 [sVCAM-1] and CRP) are altered in PCOS

and to further elucidate the effect of MET treatment on their levels. Sixty-two PCOS women and 45 normal women with similar BMI, age and waist-hip ratio were studied and 22 subjects with PCOS were put on MET 1700 mg daily for 6 months. Plasma levels of hsCRP, sICAM1 and sE-selectin were higher in PCOS group than controls. sVCAM-1 did not differ statistically between two groups. A significant reduction in hsCRP and sVCAM-1 was achieved after 6 months of MET administration: PCOS pre-treatment hsCRP 1.92 ± 0.60 versus PCOS post treatment hsCRP 0.52 ± 0.26, p = 0.005; PCOS pre-treatment sVCAM-1 668.09 ± 98.38 versus PCOS post-treatment sVCAM-1 365.82 ± 99.77, p = 0.03. This study thus demonstrated that PCOS is a state of chronic inflammation and that MET decreases the inflammatory markers in the subjects and thus has a beneficial role.

MET is recommended for women with PCOS having IGT and when lifestyle modifications fail. Endocrine society guidelines [14] do not advice use of MET as first line therapy for cutaneous manifestations of PCOS or for treatment of obesity. They recommend MET in women with PCOS who have Type 2 diabetes or IGT who fail to achieve sufficient lifestyle modification. MET is also suggested as an adjuvant therapy for infertility to prevent ovarian hyperstimulation syndrome (OHSS) in PCOS women undergoing *in vitro* fertilization (IVF) in endocrine society guidelines

Thiazolidinediones

Thiazolidinediones (TZDs; pioglitazone, rosiglitazone) introduced in the late 1990s, act by activating PPARy receptors and thereby affect various metabolic pathways though predominantly glucose. The history of this class of drugs has been very interesting with repeated withdrawals owing to adverse events. The earliest member, troglitazone, was withdrawn from market in view of fatal liver failures [39]. Rosiglitazone was initially withdrawn from market because of the data suggesting increased risk of cardiovascular events but after re-evaluation in 2013 the FDA has again allowed its prescription in the United States [40]. Similarly, pioglitazone is facing threat of extinction as the FDA has asked manufacturers to add a warning label about risk of bladder cancer [41]. Therefore, there is limited experience and data describing TZD use in women with PCOS. In a recent meta-analysis published by Li et al. [42] comparing MET and TZDs it was concluded that TZDs were superior to MET in reducing serum levels of free testosterone and DHEAS after 3 months treatment. However, the fall in BMI and serum triglycerides was more pronounced in the MET group. The authors did not observe any significant differences in ovulation, pregnancy rate, menstrual patterns, insulin sensitivity, and serum levels of androstenedione, luteinizing hormone (LH), follicle stimulating hormone (FSH), total cholesterol, LDL or insulin. Therefore, in the absence of large data MET and TZDs are not significantly different with the caveat that TZDs in animal studies have been shown to be associated with fetal loss (FDA pregnancy category C) [43].

Antiandrogens

PCOS is typified by elevation of serum androgen levels/ signs of clinical androgen excess, antiandrogens have been used in the management of PCOS symptoms.

Spironolactone

Spironolactone is an aldosterone antagonist and is primarily used as a diuretic. It has also been used in treatment of hyperandrogenism (primarily hirsutism) in PCOS patients. Zulian et al. [44] studied effects of spironolactone on clinical features, lipid profile and insulin levels in PCOS patients. Twenty-five PCOS patients (age 16-32 years; 13 lean and 12 overweight) were studied at baseline and then received oral spironolactone (100 mg/day) for 12 months; all overweight subjects were advised lifestyle modification. Clinical, endocrine and metabolic parameters (OGTT, lipid profile) were measured at baseline and at the end of the antiandrogen treatment. There was significant decline of triglycerides in overweight subjects and increased HDL-cholesterol levels in lean patients. The insulin levels at 60 min during OGTT, HOMA-IR and area under curve of insulin were also significantly lowered in overweight women after 12 months of spironolactone therapy and lifestyle changes. In overweight PCOS women long-term therapy with spironolactone combined with weight loss due to lifestyle modification had beneficial effects on glucose and lipid metabolism.

In one of our earlier papers, we studied the comparative efficacy of 6-month use of low-dose spironolactone (50 mg/day) with MET (1000 mg/day) in young women with PCOS. The results of this open-label study suggested that although both spironolactone and MET were efficacious, spironolactone appeared better than MET in the treatment of hirsutism, menstrual cycle frequency and hormonal derangements and was associated with fewer adverse events [45]. However, a Cochrane review by Brown *et al.* [46] in 2009 also showed that spironolactone is effective in decreasing the degree of hirsutism but not in treating acne vulgaris.

Flutamide

Flutamide, an oral, nonsteroidal antiandrogen has been primarily used to treat prostate cancer. It competes with testosterone and its powerful metabolite, dihydrotestosterone for binding to androgen receptors. Flutamide has also been used to treat androgen excess in women with PCOS. Gambineri et al. [47] found that obese women with PCOS, following a hypocaloric diet, responded better after addition of either MET, flutamide or the combined MET with flutamide treatment as far as the outcome regarding body fat distribution, serum androgens levels, blood lipids, hirsutism scores (HS) and menstrual patterns. Diamanti-Kandarakis et al. [48] studied the effect of flutamide on lipid profile in PCOS subjects. Seventeen PCOS subjects (ten obese and seven lean) received oral flutamide 500 mg/day for 12 weeks. Flutamide therapy was associated with significant decrease in the LDL/HDL ratio by 23% (p = 0.005), in total cholesterol by 18% (p < 0.0001), in LDL by 13% (p = 0.002) and in triglycerides by 23% (p = 0.002). Flutamide treatment was also associated with a trend toward an increase in HDL (by 14%; p = 0.14). The beneficial effect of flutamide was probably due to inhibition of androgenic actions and was found regardless of obesity. Therapy was not associated with change in weight.

Finasteride

Finasteride is a $5-\alpha$ -reductase inhibitor that inhibits the production of dihydrotestosterone. HS have been found to be low in studies of PCOS treatment with finasteride. When finasteride is used in combination with a cyproterone acetate-containing OCPs, the effect on hirsutism has been found to be better than when OCPs is used alone [49]. Finasteride also has a low side effect profile.

Cyproterone acetate

Cyproterone acetate is a synthetic steroidal antiandrogen which also acts as an agonist on progesterone receptor. In combination with ethinylestadiol it has been used in PCOS. Swiglo *et al.* conducted a systematic review and meta-ana-lysis of RCTs of antiandrogens in hirsutism [50]. They concluded that compared with placebo antiandrogens reduced Ferriman– Gallwey scores by 3.9 (95% CI 2.3–5.4). Compared with MET, spironolactone was found to reduce HS by 1.3 (CI, 0.03–2.6) and flutamide by 5.0 (CI, 3.0–7.0). Spironolactone or finasteride in combination with contraceptives or flutamide plus MET was superior to monotherapy of contraceptives or MET, respectively.

There is a risk of feminization of male fetus while treatment with antiandrogens [51]. So patients should be counseled to use contraception and avoid pregnancy while treatment with antiandrogens

Combination of antiandrogen & MET

Wu et al. [52] showed that combination of MET and contraceptive pill (containing ethinyl estradiol and

cyproterone acetate) was more effective in suppressing hyperandrogenism of obese and nonobese PCOS subjects compared with MET alone.

In a recent open-label randomized study done by our group, the efficacy of the combination of lowdose spironolactone and MET was compared with the effect of either drug alone in the management of women with PCOS. Of 204 women who met the 2006 Androgen Excess-PCOS society criteria for PCOS, 198 were randomized into three equal groups to receive MET (1000 mg/day), low-dose spironolactone (50 mg/day) or a combination of both for 6 months. A total of 169 subjects (n = 56 MET, 51 spironolactone, 62 combination) completed the study. The three groups had comparable mean age and BMI at baseline. By 6 months, menstrual cycles/year increased, whereas Ferriman-Gallwey score, serum total T and area under the curve-glucose and -insulin decreased significantly (p < 0.05) in the combination group as compared with either drug alone. There was no significant change in body weight, BMI, waist-hip ratio and blood pressure in any of the three groups. The combination group had better compliance than either drug alone, and the adverse event rate was not higher. We therefore concluded that the combination of low-dose spironolactone with MET seems superior to either drug alone in terms of clinical benefits and compliance in women with PCOS [53].

Mazza *et al.* ^[54] also found that addition of lowdose spironolactone (25 mg/day) with MET caused a more marked reduction in clinical and biochemical hyperandrogenism compared with MET alone. Fifty-six PCOS patients were randomized in two groups: group A (28 patients) was treated with MET (1700 mg/day) and group B (28 patients) was treated with MET (1700 mg/day) plus low-dose spironolactone (25 mg/day). Anthropometric, hormonal and metabolic parameters were evaluated at baseline and after 6 months of treatment. After therapy regular menses were restored in approximately 82% of group A patients (p < 0.001) and in 68% of group B patients (p < 0.001). Circulating testosterone, Δ -4-androstenedione and HS significantly decreased in both groups.

Treatment of infertility in women with PCOS Clomiphene

Endocrine society guidelines [14] recommend clomiphene citrate as first line treatment for anovulatory infertility in women with PCOS. MET is advocated as adjuvant therapy for infertility to prevent OHSS in women with PCOS undergoing IVF. Clomiphene and MET both have been studied for treatment of infertility in PCOS and it has been found that clomiphene has had improved pregnancy rates and in combination with MET had provided results comparable to injectable gonadotrophins [55]. Clomiphene alone has been found to be associated with multiple pregnancies which has been found to decrease when combined with MET. A Cochrane data review done by Tso *et al.* tested the utility of MET as co-treatment during IVF or intracytoplasmic sperm injection (ICSI) in women with PCOS. This review found MET as co-treatment before or during IVF or ICSI did not improve live birth or clinical pregnancy rates. The risk of OHSS in women with PCOS and undergoing IVF or ICSI cycles was reduced with MET (pooled OR 0.27, 95% CI 0.16–0.47) [56].

Vanky et al. did a randomized, controlled trial to see whether MET when prescribed from first trimester to delivery reduced pregnancy complications in PCOS patients. Two hundred seventy four singleton pregnancies (in 257 women with PCOS age 18-42 year) were randomly assigned to receive either MET or placebo starting from first trimester to delivery. "Preeclampsia prevalence was 7.4% in the MET group and 3.7% in the placebo group (3.7%; 95% CI, -1.7-9.2; p = 0.18). Preterm delivery prevalence was 3.7% in the MET group and 8.2% in the placebo group (-4.4%; 95%, CI, -10.1-1.2; p = 0.12). Gestational diabetes mellitus prevalence was 17.6% in the MET group and 16.9% in the placebo group (0.8%; 95% CI -8.6-10.2; p = 0.87)". No difference in fetal birth weight was found between the groups. It was concluded that there was no difference in the prevalence of pre-eclampsia, preterm delivery or gestational DM in women with PCOS treated with MET during pregnancy [57].

Therefore, clomiphene citrate remains the drug of choice for ovulation induction in PCOS-affected women desiring pregnancy. Second line intervention when clomiphene fails is exogenous gonadotropins and laparoscopic ovarian drilling (LOD). But use of gonadotropins is associated with increased risk of multiple gestations. Third line options for these patients are assisted reproductive techniques such as IVF.

Miscellaneous agents

Aromatase inhibitors have been tested for treatment of infertility in PCOS. A recent large NIH-sponsored, multicentre, double-blind, randomized, clinical trial (n = 750 subjects) has been completed demonstrating a marked superiority in live birth rate when letrozole over clomiphene is used for the treatment of anovulatory infertility in women with PCOS [58]. There are no known serious adverse events related to D-chiro-inositol therapy (an insulin sensitizer) but there are concerns about the formulation of the drug and limited evidence of its efficacy [59].

Statins have also been studied in PCOS because there has been evidence that statins reduce ovarian

androgen production. This effect may be due, at least in part, to inhibition of theca cell growth and by decreasing the concentration of precursor for production of androstenedione. Statins also have antioxidant properties. A recent Cochrane database review assessed the use of statins in PCOS women not actively trying to conceive [60]. It was shown that statins improve lipid profiles and reduce testosterone levels in women with PCOS, yet there is no beneficial effect on menstrual irregularity, hirsutism, acne or in spontaneous ovulation. Furthermore statins may increase future risk of Type 2 diabetes [61]. Statins are potentially teratogenic (pregnancy category X) and they may have serious adverse effect like myopathy.

It has been shown that dopaminergic control of LH release occurs in PCOS and cabergoline has been used in management of PCOS patients undergoing IVF for better clinical control of ovarian response and reduction in rate of OHSS without decrease in pregnancy rate. A Cochrane database review by Tang *et al.* [62] included two trials involving 230 women and showed that cabergoline appears to reduce the risk of OHSS in high-risk women, especially for moderate OHSS. Pregnancy outcome was not affected with cabergoline.

Surgical procedures

Procedures like LOD have also been used as treatment for PCOS. Previously wedge resection of the ovary was done as surgery for ovulation induction. At present minimal access procedures like LOD are used which can be done either with diathermy or laser.

Surgical procedures have been found to cause a decrease in serum LH and testosterone and androstenedione concentration [63]. This reduction in the intraovarian androgen levels allows for the development of functional follicles. Although LOD is efficacious and carries with it the benefit of multiple ovulatory cycles, relatively short operative time, a decrease in spontaneous abortions, and a lowered risk of multiple gestations, it also has disadvantages. Study by Kandil *et al.* [64] suggests that bilateral ovarian drilling may result in diminished ovarian reserve. There may also be tubo-ovarian adhesions and reduced fertility.

In a recent Cochrane review by Farquhar *et al.* [65], the effectiveness and safety of LOD was compared with ovulation induction in subfertile clomiphene resistant PCOS subjects. Live births were found in 34% of women in the LOD groups and 38% in other medical treatment groups. There was no significant difference in live birth, clinical pregnancy or miscarriage rates in the two groups. The rate of multiple pregnancies was significantly lower in the LOD group compared with trials using gonadotropins (OR 0.13; 95% CI 0.03 to 0.52; p = 0.004).

Glucagon-like peptide-1 analogues

Glucagon-like peptide-1(GLP1) analogues have also been studied in the treatment of PCOS. Kahal *et al.* [66] showed that liraglutide improves liver fibrosis markers in obese women with PCOS and nonalcoholic fatty liver disease. Jensterle *et al.* [67] showed that combined treatment with liraglutide and MET for 12 weeks was associated with significant weight loss and decrease in waist circumference in obese women with PCOS. Thirty-six patients (14 on MET 1000 mg b.i.d., 11 on liraglutide 1.2 mg once a day sc., 11 on liraglutide with MET) participated in a 12-week open-label prospective study. It was found that combination therapy was superior to liraglutide and MET monotherapy in reducing weight, BMI and waist circumference.

Phosphodiesterase 4 inhibitors

Phosphodiesterase 4 inhibitors have also been studied in PCOS. Selective inhibition of PDE4 enzyme has been implicated in the regulation of metabolism with positive effects on glucose homeostasis and weight reduction. Jensterle et al. [68] studied effect of roflumilast, a PDE4 inhibitor on body weight and hormonal and metabolic parameters in 36 obese PCOS subjects. Subjects were randomized to MET 1000 mg twice a day or combined treatment with MET 1000 mg twice a day and roflumilast 500 µg every day. BMI decreased for $1.6 \pm 1.1 \text{ kg/m}^2$ in combination arm compared with increase for $0.9 \pm 2.4 \text{ kg/m}^2$ in the MET arm (p = 0.046). Visceral adipose tissue assessed by DEXA scan also decreased significantly in combination arm. From baseline to study end, both treatment interventions resulted in a significant reduction of androstenedione (p = 0.013), free T (p = 0.002), and HOMO-IR score (p = 0.027) and a significant increase in sex hormone binding globulin (p = 0.024).

Conclusion

We conclude that treatment in women with PCOS should focus on both short- and long-term reproductive and metabolic consequences. In view of PCOS encompassing multiple specialities, a holistic approach involving general practitioners, endocrinologists, gynaecologists and health educators remains the most pragmatic approach. Though a plethora of treatment options have arrived for PCOS in recent years, the lifestyle modification including a structured meal plan and exercise schedule remains the cornerstone and the most effective modality of treatment till date. As a general rule all other treatment options are added to this depending upon the gravity of the presenting problems.

For example, OCPs would be good choice for women who do not consider fertility a concern, who have low-risk metabolic disturbances and who present predominantly with menstrual problems. Another important issue is that OCPs help to reduce unwanted teenage pregnancies especially in regions like North America. For women trying to conceive clomiphene citrate is the drug of choice and addition of MET may help to reduce OHSS and improve metabolic disturbances. Letrozole can be kept as a second line generally after clomiphene resistance. IVF remains the final option in infertile PCOS patients when other measures have failed.

Antiandrogens such as spironolactone, finasteride or flutamide can be used in hyperandrogenic subsets, although spironolactone in small doses is safe and in combination with other therapies can enhance clinical efficacy. Insulin sensitizers especially MET remains popular either alone or in various combinations. The drug, although is quite safe, has seen some resistance to its use in adolescents, pregnant women. Many treatment modalities have been proposed for PCOS-like yoga, acupuncture, chinese medicine, myoinositol, d-chiroinositol, vitamin D, etc., but there is weaker evidence for their success. Long-term data from well-designed studies involving large number of subjects may help in generating evidence regarding the treatment algorithm in women with PCOS.

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Executive summary

- Lifestyle modification (diet, exercise) is the primary intervention for management of polycystic ovary syndrome (PCOS).
- Hormonal contraception is the first line therapy for women not desiring fertility. Concerns are possible adverse effects on glucose and lipid metabolism with certain preparations and increased risk of venous thromoembolism. Not preferred in adolescent PCOS in certain countries due to social prohibitions.
- Metformin by improving insulin sensitivity reduces risk of diabetes and cardiovascular diseases in patients with PCOS. Metformin is recommended in PCOS patients with Type 2 diabetes and impaired glucose tolerance when lifestyle modifications fail. Metformin when used along with ovulation induction in IVF or ICSI reduces risk of ovarian hyperstimulation syndrome.
- Spironolactone is drug of choice for hirsutism in PCOS patients. Combination of spironolactone and metformin superior to either drug alone in terms of clinical efficacy or patient compliance.

6

• Clomiphene citrate remains drug of choice for ovulation induction in PCOS women desiring fertility. Other options are gonadotropins and assisted reproductive techniques like *in vitro* fertilization.

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Treatment of polycystic ovary syndrome: recent trial results Clinical Trial Outcomes

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