FOGSI 360
Coordinate Communicate Community
जीवनस्य वृत्तम्

FOGSI FOCUS

PCOS

PRACTICE POINTS

Algorithms for Obs & Gynae.

PCOS and Obesity

Science Integra®

MANAGEMENT OF POLYCYSTIC OVARY SYNDROME ASSOCIATED WITH OBESITY

PRACTICE POINTS

FOGSI President	: Dr. Jaydeep Tank
Moderators	: Dr. Dibyendu Banerjee, Dr. Lila Vyas
Panelists	: Dr. Bharti Kalra, Dr. Vandana Hegde, Dr. Ajay Mane, Dr. Madhuri Patel, Dr. Vinita Singh, Dr. Debmalya Sanyal, Dr. Rohan Palshetkar, Dr. Suvarna Khadilkar, Dr. Chandrika Anand, Dr. V. Padmaja

From left to right: ***Top row*** – Left to right: Dr. Bharti Kalra, Dr. Vandana Hegde , Dr. Ajay Mane, Dr. Madhuri Patel, Dr. Jaydeep Tank, Dr. Vinita Singh, Dr. Debmalya Sanyal
Bottom row –Left to right: Dr. Rohan Palshetkar, Dr. Dibyendu Banerjee, Dr. Lila Vyas, Dr. Suvarna Khadilkar, Dr. Chandrika Anand, Dr. V. Padmaja

FOGSI FOCUS
PCOS
PRACTICE POINTS
Algorithms for Obs & Gynae.

Practice points

Management of polycystic ovary syndrome associated with obesity

Dr. Jaydeep Tank*, Dr. Dibyendu Banerjee†, Dr. Lila Vyas†, Dr. Bharti Kalra‡, Dr. Vandana Hegde‡, Dr. Ajay Mane‡, Dr. Madhuri Patel‡, Dr. Vinita Singh‡, Dr. Debmalya Sanyal‡, Dr. Rohan Palshetkar‡, Dr. Suvarna Khadilkar‡, Dr. Chandrika Anand‡, Dr. V. Padmaja‡

Abstract

Polycystic ovary syndrome (PCOS) affects about 13% of premenopausal women and is characterized by symptoms such as ovarian dysfunction, androgen excess, menstrual irregularities, and infertility. Insulin resistance is a significant factor that worsens these symptoms, particularly in obese women. Management strategies for PCOS focus on a multidisciplinary approach, prioritizing lifestyle modifications like weight management and dietary changes. Pharmacological treatments, including metformin and inositols, have shown effectiveness in improving insulin sensitivity and reducing hyperandrogenism. For severe obesity, options such as anti-obesity medications and bariatric surgery can enhance metabolic health and fertility while mitigating associated comorbidities

This consensus statement, developed by a task force of ten experts in Obstetrics and Gynecology, provides a validated treatment approach for managing PCOS associated with obesity in Indian women. The task force conducted a thorough review of existing literature and utilized a structured grading system for critical appraisal, ensuring that the resulting guidelines reflect both evidence-based practices and expert clinical insights. The collaborative process involved broader deliberation with 39 additional experts, resulting in practical guidance tailored for clinicians across India.

Keywords: Polycystic ovary syndrome; premenopausal; infertilty; ovarian; obesity

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder[1] affecting ~13% of pre-menopausal women.[2] PCOS is a heterogeneous condition, of multifactorial origin including polygenic inheritance, lifestyle and environmental factors.[1,3] However, hyper pulsatile secretion of gonadotropin hormone-releasing hormone (GnRH), particularly luteinizing hormone (LH) has been implicated, as in some women with PCOS, the GnRH pulse generator was seen to be more resistant to negative feedback inhibition by progesterone and estradiol,

* President FOGSI, †Moderator for FOGSI Focus PCOS Practice Points, ‡Panel Members for FOGSI Focus PCOS Practice Points,

resulting in persistently increased GnRH pulsatility. Hyperinsulinemia, elevated insulin growth factor 1, and low sex hormone-binding globulin (SHBG) concentrations are also thought to be contributory factors.[4]

PCOS is characterized by a combination of signs and symptoms, particularly due to ovarian dysfunction and androgen excess.[1] Androgen excess can cause hirsutism, alopecia, and acne, while ovarian dysfunction can lead to chronic anovulation, oligo/amenorrhea, infertility, and endometrial hyperplasia and/or carcinoma in women with long-standing PCOS.[1, 5] Increased body mass index (BMI) is also common in women with PCOS.[1] Clinical symptoms and signs of PCOS typically start from puberty.[6]

PCOS can affect a woman's metabolism, reproductive health, and psychological well-being, and can be a risk factor for dyslipidemia, adiposity, obesity, type 2 diabetes (T2D), cardiovascular disease (CVD), infertility, pregnancy-related complications, anxiety, and depression.[2]

Scope

These key practice points aimed to develop a validated treatment approach for the clinical management of PCOS associated with obesity in Indian women.

Methodology

The task force comprised of 10 experts in the field of Obstetrics and Gynecology. The task force reviewed the existing literature and developed this consensus statement based on findings from the published literature, their clinical experience, and focused discussion within the task force. The task force members followed a well-defined grading system (Table 1) for the critical appraisal of the evidence and to grade the strength of the consensus statements. The consensus statements developed by the task force were presented to a larger group of 39 experts in Obstetrics and Gynecology. There was deliberation on each consensus point, which was later accepted, modified, or deleted. Thus, this document provides the necessary insights and useful, practical, and accurate feasible guidance to aid a practicing clinician across the country.

Table 1. Level of evidence and grading strength of recommendations

Level of evidence	Description
Level A	Data derived from multiple randomized trials or meta-analyses or evidence-based clinical practice guidelines
Level B	Data derived from a single randomized trials or large non-randomized trial
Level C	The consensus of experts or small studies, retrospective studies or registries or narrative/literature reviews
Level D	Data derived from Clinical experience
Class of recommendations	
Class I	Evidence and or general agreement that a given treatment or procedure is beneficial, useful or effective. It is recommended
Class IIa	Evidence is in favour of efficacy/ usefulness and should be considered
Class IIb	Efficacy/usefulness is less well established, and recommendations may be considered.
Class III	Evidence and or general agreement that a given treatment or procedure is not beneficial, useful or effective and in some cases may cause harm. Not recommended.

Obesity as a risk factor for the development of PCOS

Insulin resistance/ hyperinsulinemia is a cause and effect of androgen excess, which contribute to hyperandrogenic features in women with PCOS through effects within the ovary.[7] Weight gain and obesity can also increase androgen secretion in women with PCOS through its effects on insulin resistance and adipokine release. Most women with PCOS (38–88%) are overweight or obese.[8]

Significantly increased weight gain (around the waist/ central obesity), especially in adolescence and early adulthood and obesity are risk factors for the development of PCOS later in life.[8,9] Long-term weight gain, most especially in early adulthood between ages 14 and 31 years, was significantly

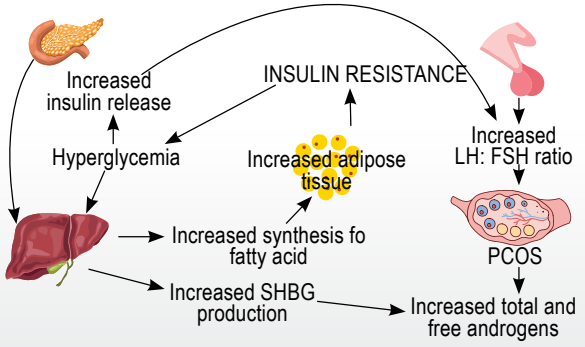
greater in women with PCOS diagnosed with T2DM by age 46 years. An increase of BMI between 14 and 31 years of age was observed to be greater in women with isolated oligo/amenorrhea (p=0.006), oligo/amenorrhea, and hirsutism (p=0.001), and diagnosis of PCOS (p=0.001) than in women without PCOS symptoms or diagnosis.[10]

PCOS, insulin resistance, and obesity

A key pathophysiological feature of PCOS is insulin resistance, which leads to abnormalities in fatty acid metabolism,[4] hyperandrogenism, and worsened clinical presentation of PCOS.[2] In fact, most women with PCOS (50–90%) are insulin resistant.[8] Excessive weight can exacerbate insulin resistance leading to hyperinsulinemia, which can further increase androgen production. Women with PCOS have a higher rate of weight gain and development of obesity. Hence, key targets in PCOS management include improving insulin resistance and excess adiposity.[2]

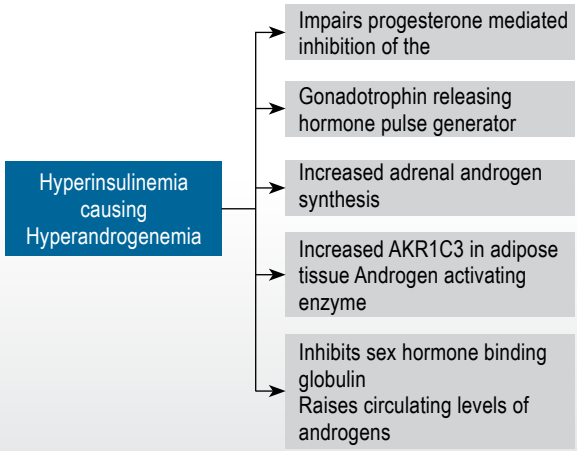
The hyperandrogenism and insulin resistance exacerbate one another (Figure 1). Hyperandrogenism and insulin resistance together contribute to the pathophysiology (Figure 2), but their contributions differ from patient to patient, which accounts for the heterogeneous nature of PCOS and its presentation.[11]

Figure 1. Pathophysiology of Insulin resistance in PCOS[12]



Picture courtesy : Pathophysiology of PCOS -Manu, Thomson Soni, Victoria and Pranav Kumar Prabhakar

Figure 2. Pathophysiology of hyperinsulinemia in causing hyperandrogenemia[13]



Phenotypic peculiarities among Indian women with PCOS

The Rotterdam criteria is commonly used to diagnose PCOS, with the presence of any two of the following three features indicative of PCOS: 1) Oligo/anovulation (O); 2) Clinical and/or biochemical hyperandrogenemia (H); and 3) Polycystic ovaries on ultrasound (P), with the exclusion of other known disorders of hyperandrogenemia. Hence, four possible phenotypes can exist: Phenotype A—P + H + O (PCOS complete); phenotype B—H + O; phenotype C—H + P; phenotype D—O + P.[14]

In an observational study on Indian women with PCOS, the prevalence of PCOS was found to be the highest for those with phenotype A (HPO; 52.6%), followed by those with phenotype D (OP; 21%), phenotype C (HP; 15.1%), and phenotype B (HO; 11.4%).[15, 16, 17] Common clinical features included menstrual irregularities (84.9%), weight gain (overweight/obese; 60.3%), higher waist-to-hip ratio, and hirsutism (56.0%).[15]

An observational study on North Indian women with PCOS reported phenotypic differences in biochemical, hormonal, and clinical parameters

among North Indian women, with those from Delhi having significantly higher BMI (p=0.01), glucose intolerance, insulin resistance (p=0.006), and insulin sensitivity (p=0.03), while those from Srinagar having higher fasting glucose (p=0.01) and serum total testosterone (p=0.01) levels. Two clear phenotypes were evident in this study, which were obese hyperinsulinemia dysglycemic and lean hyperandrogenic.[18]

Another observational study reported an association between calorie-dense diet, high BMI, insulin resistance, hirsutism, and higher serum anti-Mullerian hormone (AMH) concentrations in Indian women with PCOS.[19] Identifying the PCOS phenotype during diagnosis can be useful in formulating individualized treatment plans.

Insulin resistance and fat distribution

Insulin resistance is defined as a pathological condition characterized by decreased responsiveness or sensitivity to the metabolic actions of insulin.[20]

IR in PCOS reflects the interaction of genetic influences, non-heritable intra-and extrauterine environmental factors, and alternative adaptations to energy excess. IR is primarily observed in skeletal muscle, adipose tissue, and liver.[21] Insulin resistance is documented on clamp studies in 75% of lean women and 95% of women with a higher BMI• [22]

Evidence suggests that insulin resistance in PCOS may be due to an intrinsic defect in post-receptor insulin signaling (inositol-containing phosphoglycan mediators)[23] in adipocytes and myocytes.[24] Additionally, insulin may also mediate steroidogenic effects through the mitogen-activated protein kinase pathway. These signaling pathways are a key component of PCOS pathogenesis and underlie the association between weight-gain and obesity with PCOS. In fact, weight loss has been seen to improve PCOS symptoms in overweight and obese women through a corresponding improvement in insulin sensitivity and serum insulin levels.[8]

In PCOS, compensatory hyperinsulinemia due to insulin resistance can also affect lipid metabolism in peripheral tissues through increased adipokine and fatty acid release.[8] A large meta-analysis (>3,400 women with PCOS) observed significantly lower adiponectin levels compared with BMI-adjusted control women, which was found to be associated with insulin resistance.[25] There may also be abnormalities in the lipolytic functioning of adipocytes in women with PCOS, due to changes in the function of the post-receptor protein kinase A – hormone-sensitive lipase complex.[6,8]

Both visceral and subcutaneous fat may contribute to insulin resistance.[8,26] A study on nonobese Swedish women with PCOS observed increased catecholamine-induced lipolysis in visceral fat cells,[6] while a study on Indian women with PCOS observed that subcutaneous abdominal fat volume and not visceral fat was independently associated with insulin resistance. Additionally, the waist circumference of women with PCOS correlated closely with subcutaneous, visceral, and total fat volumes.[26]

Overweight and obese women with PCOS are at increased risk of T2 Diabetes mellitus

PCOS is associated with increased risk of prediabetes (impaired fasting glucose or impaired glucose tolerance) and T2D in a meta-analysis.[27] Overweight and obesity have a synergistic effect on the development of T2D. In a prospective, population-based cohort study, overweight/ obese women with PCOS (BMI ≥25.0 kg/m^2) were found to have a significantly higher risk of developing T2D compared with overweight/obese controls (odds ratio = 2.45), while women with normal weight and PCOS did not have an increased risk of prediabetes or T2D. Weight gain in early adulthood (14–31 years of age), in particular, was significantly greater in women with

PCOS developing T2D than in those with normal glucose tolerance and PCOS ($p<0.001$).[10]

Management strategies for PCOS and obesity

Management of PCOS involves a multidisciplinary approach.[1] International evidence-based guidelines suggest management of weight and lifestyle (behavior, diet, and physical activity, also called Lifestyle intervention) as first-line therapy for PCOS.[1,2] Sleep and psychological interventions, as well as a variety of traditional, complementary, and integrative medicine approaches for optimal management of PCOS have also been investigated.[2]

Weight loss and alternative therapies for PCOS

A systematic review reported that weight loss led to a greater reduction in insulin resistance, increased menstrual regularity, and improved hyperandrogenism, ovulation, and pregnancy rate in women with PCOS that was independent of diet composition. Hence, targeting weight loss in all overweight women with PCOS is recommended.[28]

Apart from lifestyle intervention, which should be recommended in all patients with PCOS, many medications have been used in the management of PCOS. Pharmacotherapy includes hormonal and non-hormonal medicines.[29]

Medicines, that are effective in reducing Insulin resistance, include Metformin, and inositols. Inositol supplementation and metformin are beneficial in reducing hyperandrogenism and improving metabolic profiles.[2] Inositols are second messengers responsible for intracellular glucose transport, that increases GLUT4 translocation to the cell membrane.[30]

Efficacy of myoinositols in PCOS

Myoinositol, an isoform of inositol, is a carbocyclic sugar belonging to the vitamin B complex that has been investigated for the management of PCOS.[23,30] A key factor in the pathogenesis of PCOS is thought to be a deficiency of inositols, as an increased urinary excretion leading to its deficiency, has been observed in women with PCOS.[31]

Inositol acts as a secondary messenger with a role in insulin signaling transduction.There are nine stereo-isomers of inositol of which myo-inositol (MI) is the most abundant in the human body. MI promotes glucose uptake and is also involved in FSH mediated pathways impacting proliferation and maturation of granulosa cells. MI is also postulated to enhance aromatase synthesis in granulosa cells and therefore reducing androgen production.[22] In recent times, MI has emerged as a safe alternative approach to therapy for patients with PCOS, both in cases of infertility and in younger individuals.[32]

Although a recent systematic review and meta-analysis suggest that the evidence on the use of inositol in the management of PCOS is limited and inconclusive, the authors conclude that substantial evidence exists to encourage its use.[38] Table 2 provies evidences stating the efficacy of inositol and/or metformin in the management of PCOS.

Metformin in obese patients with PCOS

Metformin is an antidiabetic medication commonly used to treat type 2 diabetes mellitus (T2DM) and prediabetes (insulin resistance). It functions as an insulin sensitizer, aiding in weight loss and improving metabolic health. Metformin is particularly beneficial for individuals at high metabolic risk, such as those with diabetes risk factors, impaired glucose tolerance, or belonging to high-risk ethnic groups like Indians.[42]

For managing PCOS in overweight or obese women, or in women with impaired glucose tolerance (IGT) and diabetes, metformin therapy can be initiated with a starting dose of 500 mg once or twice daily in an immediate-release oral formulation. The daily dosage is often increased weekly in 500 mg increments to reduce gastrointestinal (GI) side effects. The suggested

Table 2. Evidences stating the efficacy of inositol and/or metformin in the management of PCOS		
Type of study	**Method**	**Results**
Myo-inositol (MI) vs. placebo:[22] Inositol (100 mg) twice daily for 14 weeks[22]		MI improves weight, BMI, testosterone, androstenedione,fasting insulin, insulin area under the curve and HOMA-IR Increase in ovulation frequency ($p<0.01$), weight loss ($p<0.01$)
MI vs. metformin[22]		MI has fewer gastrointestinal adverse effects than metformin. MI was superior to metformin in cycle regulation. Metformin was superior to MI for fasting insulin, WHR, WC, and mFG score (low to moderate certainty).
MI + metformin[22]	1 study - 100 patients RCT- Myoinositol group received 1 g twice daily while Metformin group received 500 mg twice daily for 6 months	MI + DCI to metformin is better than metformin alone for cycle regularity and lipids. Treatment with myoinositol and metformin both decreased body mass index, androgenic features, improved menstrual abnormalities and polycystic o ovaries MET and MI are comparable in their effects on clinical, hormonal, and biochemical profiles. MI, however, had a better safety profile and tolerance due to minimal side effects compared to MET. These results demonstrate the potential role of MI as a novel asset in the armamentarium in the management of PCOS.
MI vs. DCI[22]		MI improves clinical pregnancy rate and total pregnancy rate vs. DCI
MI + DCI + metformin vs. metformin[22],33		Improvements in menstrual regularity and lipid profile were observed with the inositol-containing combination.
	RCT, thrice daily administration of Metformin+ MI vs. Metformin alone	In a study, the live birth rates were significantly higher in the group treated with Metformin (500 mg) plus Myoinositol (600 mg) as compared to metformin alone [55% (33/60); 26.67% (16/60); $p=0.002$].
Only Inositols	Twice daily administration of myoinositol (1 g)[34]	Myoinositol decreased insulin resistance (HOMA index), BMI, androgenic features, and improved polycystic ovaries and menstrual abnormalities after 6 months of treatment. It also led to a reduction in oily skin, hirsutism, and acne.
	Daily myo-inositol 2 g plus folic acid 200 mug[35]	After 12 weeks of MYO administration, plasma LH, PRL, T, insulin levels and LH/FSH significantly reduced. Insulin sensitivity, expressed as a glucose-to-insulin ratio and HOMA index, significantly improved after 12 weeks of treatment. Menstrual cyclicity was restored in all amenorrheic and oligomenorrheic subjects.
		Myoinositols had a better safety profile and tolerance due to minimal side effects compared to metformin.[36]
	Metformin Or Myoinositol Or metformin+ myoinositol twice daily[37]	Reduction in AMH in all groups of insulin sensitizers with a significant fall in the metformin-only group. Cycle regularity, reduction in AFC, mFGS, and grade of acne were also obtained.
	Inositols for PCOS, A Meta analysis, 2024 Thirty trials (n = 2230; 1093 intervention, 1137 control), with 19 pooled in meta-analyses.[38]	Thirteen comparisons were assessed, with 3 in meta-analyses. Evidence suggests benefits for myo-inositol or D-chiro-inositol (DCI) for some metabolic measures and potential benefits from DCI for ovulation. Myo-inositol likely causes fewer gastrointestinal adverse events compared with metformin.
	RCT n=50 Metformin 1500 mg/day or Myoinositol 4 gm/ day[39]	The insulin sensitivity improved in both treatment groups. The BMI significantly decreased and the menstrual cycle was normalized in about 50% of the women. No significant changes in acne and hirsutism were observed.
	Inositol twice a day[40]	The effect of inositol on follicular maturation was rapid, because the circulating concentration of E2 increased only in the inositol group during the first week of treatment. Significant ($p<0.01$) weight loss (and leptin reduction) was recorded in the inositol group, whereas in the placebo group was recorded an increase of the weight ($p<0.05$). A significant increase in circulating high-density lipoprotein was observed only in the inositol-treated group.
	MI or metformin[32]	• MI has emerged as a safe alternative approach to therapy for patients with PCOS, both in cases of infertility and in younger individuals • Statistically significant decrease in the mean values of FSH, testosterone, androstenedione, DHEAS, FAI, SHBG, HOMA-IR, and fasting insulinaemia after therapy in both groups was observed.
	Daily administration of myoinositol (1 g) and alpha lipoic acid (400 mg) for ≥12 weeks[41]	Significant decrease in HOMA index ($o<0.05$) and glucose-induced insulin response ($p<0.05$) and thus improved insulin sensitivity in obese women with PCOS.

maximum daily dose is 2.5 g in adults and 2 g in adolescents.[43]

Metformin is generally considered safe and well-tolerated. However, gastrointestinal side effects, such as diarrhea, nausea, and vomiting, are common, affecting up to 30% of patients. Less frequent side effects include chest discomfort, headache, sweating, low blood sugar, weakness, and rhinitis. Long-term use of metformin has been associated with decreased vitamin B12 levels, which should be monitored, particularly in patients with anemia or peripheral neuropathy, as vitamin B12 supplementation may be necessary.[42]

Metformin is contraindicated in individuals with severe renal dysfunction, hypersensitivity to metformin, or metabolic acidosis.[44]

Metformin (500 mg, thrice a day) has been observed to reduce body weight and decrease androgen levels by increasing insulin sensitivity and peripheral glucose uptake and decreasing insulin-induced suppression of peripheral fatty acid oxidation.[45]

Metformin and myoinositol in obese patients with PCOS

Metformin and myoinositol vary in their mechanisms of action in improving insulin resistance and hyperinsulinemia; hence, it is hypothesized that both drugs in combination may have a synergistic effect in managing hyperinsulinemia in women with PCOS, with lower doses of each drug resulting in similar efficacy.[30]

Anti-Obesity medications in PCOS

Orlistat

Orlistat is a reversible inhibitor of lipases, exerts its therapeutic activity in the lumen of the stomach and small intestine, by binding covalently to the active serine residue site of gastric and pancreatic lipases. It reduces fat absorption and helps with weight loss.[52]

Weight reduction is reported to begin within 2 weeks of initiating orlistat. Statistically significant weight loss was observed after orlistat use for over 2 months. The mean weight loss in patients by the

Indian studies	Dosage of Metformin- Myoinositol combination	Results observed
Nagaria et al conducted a Prospective study on 70 Indian women with PCOS[30]	Metformin (500 mg) and myoinositol (600 mg) for 3 months	• Improvement in menstrual complaints in >90% of women and 25% of women with infertility conceived during the study • Improvement in acne, oily skin, and hirsutism were reported by >66%, 50%, and 29% of women, respectively.
RCT conducted in Indian women [46]	Myoinositol (1 g/day) plus metformin (1000 mg/day) -4 months	• Reduced body weight • Reduced fasting insulin • Improved menstrual cycles and fertility
RCT conducted in South Indian women [47]	Metformin (500 mg) and myoinositol (1.1 g) with D-chiro-inositol (27.6 mg) twice daily	• Improved cycle regularity
Prospective study in Indian women[48,49]	Twice daily metformin (500 mg) plus myoinositol (2 g) after 24 weeks of treatment vs. metformin (500 mg, thrice a day) or myoinositol (2 g, twice a day) alone.	• Significant improvement in reduction of BMI, serum LH, FSH, LH/FSH ratio, free and total testosterone, insulin levels • Improved cycle regularity • Reduced PCOM, acne and hirsutism
Infertile Indian women with PCOS with raised AMH levels (>5 ng/ml). [37]	Metformin (850 mg) plus myoinositol (2 g) for 3 months	• Reduced AMH levels, hirsutism, and acne, and regularized the menstrual cycle
RCT involving Indian women with PCOS undergoing ovulation induction[50]	Metformin (500 mg) plus myoinositol (600 mg) thrice daily	• Improved menstrual cycle length and bleeding days, and live birth rate
Infertile Indian women with PCOS[51]	Myoinositol (600 mg) plus metformin (500 mg) thrice a day	• Among those with a family history of T2D, the pregnancy rate was higher with the metformin-myoinositol combination treatment

end of 6 months of orlistat use was observed to be approximately 5.6 kg, whereas those in the placebo group show a weight loss of only 2.4 kg.[53]

Glucagon-like peptide-1 (GLP-1) agonists

The role of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has been investigated in the metabolic management of PCOS.[51] GLP-1 RAs are reported to be efficacious in reducing glycated hemoglobin levels and promoting weight loss while reducing hyperlipidemia.[54] Most RCTs reported superior weight loss with GLP-1 RAs compared to lifestyle changes or metformin along with metabolic, cardiovascular, and reproductive benefits in women with PCOS.[55]

A systematic review identified liraglutide and exenatide alone or in combination with metformin as better options among GLP-1 RAs for the treatment of PCOS.[56] Another systematic review reported that liraglutide significantly reduced BMI and serum testosterone levels (p=0.0003) in women with PCOS after 3 months of treatment.[57]

In an RCT, 26 weeks of liraglutide treatment (1.8 mg/day) significantly reduced body weight, liver fat content, visceral adipose tissue, and the prevalence of nonalcoholic fatty liver disease (all p<0.01) in women with PCOS.[58] A study observed that combination treatment with metformin (1000 mg, twice a day) and low-dose liraglutide (1.2 mg, once a day) significantly increased *in vitro* fertilization pregnancy rate compared with metformin (1000 mg, twice a day; p=0.03) alone.[59]

A study has shown that treatment with semaglutide, at low doses, significantly reduced body weight in almost 80% of obese PCOS patients who were unresponsive to a previous lifestyle plan. It was also associated with the normalization of menstrual cycles.[60]

Recommendations will only apply to adults who are overweight and not adolescents. There were no studies identified in adolescents. This is a high priority area for clinicians and those with PCOS and this is a high priority area for future research.

Role of bariatric/ metabolic surgery for obesity in PCOS

Bariatric surgery in women with obesity and PCOS improved metabolic outcomes with greater improvement in anthropometric measures (weight, BMI, waist circumference, hip circumference, W/H), hormonal measures (total testosterone, FAI), metabolic measures (fasting glucose, fasting insulin, triglycerides, LDL-cholesterol, and hemoglobin A_{1C}, with very low certainty of evidence.[61]

A recent large single-center prospective cohort study was published in 993 women with PCOS showing dramatic improvement in hirsutism, menstrual irregularity, and associated comorbidities [T2D (79.7%), hypertension (78.7%), sleep apnea (98.5%)] and symptoms of PCOS were statistically (0.0001) reduced at follow-up.[62]

Guidelines recommend surgery to aid weight loss with a BMI > 35 kg/m² and potentially for a BMI between 30- 34.9 kg/m² with associated metabolic co-morbidity. Vertical Sleeve Gastrectomy and Roux-en-Y gastric bypass are the most common weight loss surgeries and are usually minimally invasive with low morbidity and mortality.[22]

In PCOS, pregnancy issues are relevant with weight loss appearing to improve ovulation and fertility and reduce pregnancy comorbidities. However, bariatric/metabolic surgery can cause nutrient deficiencies important for fetal development and increases perinatal mortality, pre-term birth, and small for gestational age babies.[22]

Practice points

- Insulin resistance and hyperinsulinemia are interrelated with hyperandrogenism, and women with dyslipidemia, weight gain in early adulthood, and women with obesity, are at risk of developing PCOS. (Class I, Level B).
- Insulin resistance and hyperandrogenism exacerbate each other in PCOS. (Class I, Level B).
- Reducing insulin resistance and excess weight can be considered as key targets in PCOS management (Class I, Level A).
- Phenotypical classification of PCOS is useful in making individualized treatment plans for women with PCOS. (Class IIa, Level C).
- Weight loss should be advised in overweight and obese women to improve PCOS symptoms, insulin sensitivity, and serum insulin levels (Class I, Level A).
- All women with PCOS are at increased risk of prediabetes and T2DM, especially women who are overweight or obese; hence tests for glucose intolerance should be monitored at first visit and at regular intervals. (Class I, Level A).
- Myoinositol, part of the vitamin B complex, is a safe therapeutic approach and could be considered for women with PCOS (Class I, Level A).
- Inositol (in any form) could be considered in women with PCOS based on individual preferences and values, noting limited harm, potential for improvement in metabolic measures, (Class 1, Level A).
- Metformin, an insulin-sensitizer drug, can reduce body weight in obese patients with PCOS and decrease androgen levels (Class I, Level A).
- Metformin alone should be considered in adults with PCOS and a BMI ≥ 25 kg/m2 for anthropometric, and metabolic outcomes including insulin resistance, glucose, and lipid profiles.
- Where COCP is contraindicated, not accepted or not tolerated, metformin may be considered for irregular menstrual cycles.
- Metformin in combination with Myoinositol could be an effective treatment for managing PCOS (Class I, Level A).
- Metformin in combination with Myoinositol in obese patients with PCOS has demonstrated better improvement in hormonal and metabolic parameters compared to metformin or myoinositol alone (Class I, Level A).
- Metformin in combination with Myoinositol can regularize the menstrual cycle and improve several PCOS symptoms in obese women, including ovarian function, LH/FSH ratio, serum androgens, SHBG, and serum total and free testosterone (Class I, Level A).
- Anti-obesity medications including liraglutide, semaglutide, both glucagon-like peptide-1 (GLP-1) receptor agonists and orlistat, could be considered, in addition to active lifestyle intervention, for the management of higher weight in adults with PCOS as per general population guidelines.

Practice points

- Strong consideration should be given to GLP-1 RAs when identifying treatment strategies for women with PCOS who are overweight or obese and glucose intolerant /diabetes have CVD or other risk factors. (Class I, Level A).
- Avoid pregnancy during treatment with anti-obesity medications.
- Anti-obesity medications should be avoided in adolescents.
- Bariatric/metabolic surgery could be considered to improve weight loss, hypertension, diabetes (prevention and treatment), hirsutism, irregular menstrual cycles, and ovulation and pregnancy rates in women with PCOS.
- Pregnancy should be avoided for 1 year until stable weight is achieved.

References

1. Escobar-Morreale HF. Polycystic ovary syndrome: Definition, aetiology, diagnosis and treatment. Nat Rev Endocrinol. 2018;14(5):270–284.
2. Cowan S, Lim S, Alycia C, et al. Lifestyle management in polycystic ovary syndrome - Beyond diet and physical activity. BMC Endocr Disord. 2023;23(1):14.
3. Parker J, O'Brien C, Hawrelak J, Gersh FL. Polycystic Ovary Syndrome: An Evolutionary Adaptation to Lifestyle and the Environment. Int J Environ Res Public Health. 2022 Jan 25;19(3):1336.
4. Witchel SF. Puberty and polycystic ovary syndrome. Mol Cell Endocrinol. 2006;254-255:146-153.
5. Legro RS. Evaluation and Treatment of Polycystic Ovary Syndrome. [Updated 2017 Jan 11]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK278959/
6. Ek I, Arner P, Rydén M, et al. A unique defect in the regulation of visceral fat cell lipolysis in the polycystic ovary syndrome as an early link to insulin resistance. Diabetes. 2002;51(2):484-492.
7. Baptiste CG, Battista MC, Trottier A, et al. Insulin and hyperandrogenism in women with polycystic ovary syndrome. J Steroid Biochem Mol Biol. 2010; 122(1-3):42–52.
8. Barber TM, Hanson P, Weickert MO, Franks S. Obesity and polycystic ovary syndrome: Implications for pathogenesis and novel management strategies. Clin Med Insights Reprod Heal. 2019;13:1179558119874042.
9. Ollila M-ME, Piltonen T, Puukka K, et al. Weight gain and dyslipidemia in early adulthood associate with polycystic ovary syndrome: Prospective Cohort Study. J Clin Endocrinol Metab. 2016;101(2):739–747.
10. Ollila MM, West S, Keinänen-Kiukaanniemi S, et al. Overweight and obese but not normal weight women with PCOS are at increased risk of Type 2 diabetes mellitus-a prospective, population-based cohort study. Hum Reprod. 2017; 32(2):423–431.
11. Harada M. Pathophysiology of polycystic ovary syndrome revisited: Current understanding and perspectives regarding future research. Reprod Med Biol. 2022; 21(1): e12487
12. Manu, Soni T, Victoria, Prabhakar PK. Pathophysiology of polycystic ovarian syndrome. 2022; IntechOpen. doi: 10.5772/intechopen.101921
13. Dong J, Rees DA. Polycystic ovary syndrome: Pathophysiology and therapeutic opportunities. BMJ Med. 2023; 2(1): e000548.
14. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004; 19(1):41–47.
15. Khanorkar N, Kulkarni P, Warjukar E. Prevalence and phenotypic diversity of PCOS in Indian women: An observational study. Int J Sci Res. 2023; 12(10):738–48.
16. Kar S. Anthropometric, clinical, and metabolic comparisons of the four Rotterdam PCOS phenotypes: A prospective study of PCOS women. J Hum Reprod Sci. 2013; 6(3):194–200.
17. Bharali MD, Rajendran R, Goswami J, et al. Prevalence of Polycystic Ovarian Syndrome in India: A Systematic Review and Meta-Analysis. Cureus. 2022;14(12):e32351.
18. Ganie MA, Marwaha R, Dhingra A, et al. Observation of phenotypic variation among Indian women with polycystic ovary syndrome (PCOS) from Delhi and Srinagar. Gynecol Endocrinol. 2016;32:1–5.
19. Kulkarni SD, Patil AN, Gudi A, et al. Changes in diet composition with urbanization and its effect on the polycystic ovarian syndrome phenotype in a Western Indian population. Fertil Steril. 2019;112(4):758-763.
20. Wilcox G. Insulin and insulin resistance. Clin Biochem Rev. 2005; 26(2): 19–39.
21. Ibáñez L, Oberfield SE, Witchel S et al. An International Consortium Update: Pathophysiology, Diagnosis, and Treatment of Polycystic Ovarian Syndrome in Adolescence. Horm Res Paediatr. 2017; 88 (6): 371–395.
22. Helena Teede et al. International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome 2023. Monash Universityhttps://doi.org/10.26180/24003834.v1
23. Papaleo E, Unfer V, Baillargeon JP, et al. Myo-inositol in patients with polycystic ovary syndrome: a novel method for ovulation induction. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2007;23(12):700–703.
24. Diamanti-Kandarakis E, Papavassiliou AG. Molecular mechanisms of insulin resistance in polycystic ovary syndrome. Trends Mol Med. 2006;12(7):324–32.
25. Toulis KA, Goulis DG, Farmakiotis D, et al. Adiponectin levels in women with polycystic ovary syndrome: a systematic review and a meta-analysis. Hum Reprod Update. 2009;15(3):297–307.
26. Kalra P, Bansal B, Nag P, et al. Abdominal fat distribution and insulin resistance in Indian women with polycystic ovarian syndrome. Fertil Steril. 2009;91(4 Suppl):1437–40.
27. Moran LJ, Misso ML, Wild RA, et al. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: A systematic review and meta-analysis. Hum Reprod Update. 2010;16(4):347–63.
28. Moran LJ, Ko H, Misso M, et al. Dietary composition in the treatment of polycystic ovary syndrome: a systematic review to inform evidence-based guidelines. Hum Reprod Update. 2013;19(5):432.
29. Rashid R, Mir SA, Kareem O et al. Polycystic ovarian syndrome-current pharmacotherapy and clinical implications. Taiwan J Obstet Gynecol. 2022; 61(1):40–50.

30. Nagaria T, Mohapatra A, Jaiswal J. Effect of myoinositol and metformin in combination on clinical and hormonal profile in patients of polycystic ovarian syndrome. Int J Reprod Contracept Obs Gynecol. 2019;8(2):702-709.
31. Baillargeon J-P, Diamanti-Kandarakis E, Ostlund REJ, et al. Altered D-chiro-inositol urinary clearance in women with polycystic ovary syndrome. Diabetes Care. 2006;29(2):300-305.
32. Gudović A, Bukumiric Z, Milincic M et al. The Comparative Effects of myo-inositol and metformin therapy on the clinical and biochemical parameters of women of normal weight suffering from polycystic ovary syndrome. Biomedicines. 2024; 12(2): 349.
33. Agrawal A, Mahey R, Kachhawa G et al. Comparison of metformin plus myoinositol vs metformin alone in PCOS women undergoing ovulation induction cycles: randomized controlled trial. Gynecol Endocrinol. 2019; 35(6):511-514.
34. Angik R, Jajoo SS, Hariharan C et al. A comparative study of metabolic and hormonal effects of myoinositol vs. metformin in women with polycystic ovary syndrome: A randomised controlled trial. Int J Reprod Contracept Obstet Gynecol. 2015 Feb;4(1):189-194
35. Genazzani AD, Lanzoni C, Ricchieri F et al. Myo-inositol administration positively affects hyperinsulinemia and hormonal parameters in overweight patients with polycystic ovary syndrome. Gynecol Endocrinol. 2008; 24(3):139-44.
36. Bodepudi R, Seher S, Khan SA et al. Myoinositol Versus Metformin in the Treatment of Polycystic Ovarian Syndrome: A Systematic Review. Cureus. 2023 Jul; 15(7): e41748.
37. Chhabra N, Malik S. Effect of insulin sensitizers on raised serum anti-mullerian hormone levels in infertile women with polycystic ovarian syndrome. J Hum Reprod Sci. 2018 Oct-Dec; 11(4): 348–352.
38. Fitz V, Graca S, Mahalingaiah S et al. Inositol for Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis to Inform the 2023 Update of the International Evidence-based PCOS Guidelines. J Clin Endocrinol Metab. 2024; 109(6):1630–55.
39. Fruzzetti F, Perini D, Russo M et al. Comparison of two insulin sensitizers, metformin and myo-inositol, in women with polycystic ovary syndrome (PCOS). Gynecol Endocrinol. 2017; 33(1):39–42.
40. Gerli S, Mignosa M, Di Renzo GC. Effects of inositol on ovarian function and metabolic factors in women with PCOS: a randomized double-blind placebo-controlled trial. Eur Rev Med Pharmacol Sci. 2003;7(6):151–59.
41. Genazzani AD, Despini G, Santagni S et al. Effects of a combination of alpha lipoic acid and myo- inositol on insulin dynamics in overweight/ obese patients with PCOS. Endocrinol Metab Synd. 2014; 3:40.
42. Drzewoski J, Hanefeld M. The current and potential therapeutic use of metformin-The good old drug. Pharmaceuticals (Basel). 2021; 14(2):122.
43. Naderpoor N, Shorakae S, de Courten B. Metformin and lifestyle modification in polycystic ovary syndrome: Systematic review and meta-analysis. Human Reproduction Update. 2015; 21 (5): 560–74
44. Corcoran C, Jacobs TF. Metformin. Treasure Island (FL): StatPearls Publishing; 2024
45. Kolodziejczyk B, Duleba AJ, Spaczynski RZ et al. Metformin therapy decreases hyperandrogenism and hyperinsulinemia in women with polycystic ovary syndrome. Fertil Steril. 2000; 73(6):1149–54.
46. Chirania; K; Mishra, S; Behera S. A randomised clinical trial comparing myoinositol and metformin in PCOS. Int J Reprod Contracept Obs Gynecol. 2017;6(5):1814–20.
47. Nazirudeen R, Sridhar S, Priyanka R, et al. A randomized controlled trial comparing myoinositol with metformin versus metformin monotherapy in polycystic ovary syndrome. Clin Endocrinol (Oxf). 2023;99(2):198–205.
48. Shivani, D; Sravanthi, P; Naga J. Comparative study on efficacy of myo inositol over metformin in Polycystic ovary syndrome patients. Int J Reprod Contracept Obs Gynecol. 2021;10(5):1899–1905.
49. Swarnalatha S, Ramya S, Rajesh R, et al. A randomized controlled trial comparing myo-inositol with metformin in patients with polycystic ovary syndrome. Int J Nov Res Dev. 2023;8(12).
50. Agrawal A, Mahey R, Kachhawa G, Khadgawat R, Vanamail P, Kriplani A. Comparison of metformin plus myoinositol vs metformin alone in PCOS women undergoing ovulation induction cycles: randomized controlled trial. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2019;35(6):511-514.
51. Prabhakar P, Mahey R, Gupta M, et al. Impact of myoinositol with metformin and myoinositol alone in infertile PCOS women undergoing ovulation induction cycles - randomized controlled trial. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2021;37(4):332-336.
52. Heck AM, Yanovski JA, Calis KA et al. Orlistat, a New Lipase Inhibitor for the Management of Obesity. Pharmacotherapy. 2000; 20(3): 270–279.
53. Bansal AB, Patel P, Khalili YA. Orlistat. Treasure Island (FL): StatPearls Publishing; 2024
54. Szczesnowicz A, Szeliga A, Niwczyk O, Bala G, Meczekalski B. Do GLP-1 Analogs Have a Place in the Treatment of PCOS? New Insights and Promising Therapies. J Clin Med. 2023;12(18).
55. Jensterle M, Herman R, Janež A. Therapeutic Potential of Glucagon-like Peptide-1 Agonists in Polycystic Ovary Syndrome: From Current Clinical Evidence to Future Perspectives. Biomedicines. 2022;10(8).
56. Siamashvili M, Davis SN. Update on the effects of GLP-1 receptor agonists for the treatment of polycystic ovary syndrome. Expert Rev Clin Pharmacol. 2021;14(9):1081-1089.
57. Niafar M, Pourafkari L, Porhomayon J, Nader N. A systematic review of GLP-1 agonists on the metabolic syndrome in women with polycystic ovaries. Arch Gynecol Obstet. 2016;293(3):509-515.
58. Frøssing S, Nylander M, Chabanova E, et al. Effect of liraglutide on ectopic fat in polycystic ovary syndrome: A randomized clinical trial. Diabetes Obes Metab. 2018;20(1):215-218.
59. Salamun V, Jensterle M, Janez A, Vrtacnik Bokal E. Liraglutide increases IVF pregnancy rates in obese PCOS women with poor response to first-line reproductive treatments: a pilot randomized study. Eur J Endocrinol. 2018;179(1):1-11.
60. Carmina E, Longo RA. Semaglutide treatment of excessive body weight in obese PCOS patients unresponsive to lifestyle programs. J Clin Med. 2023; 12(18): 5921.
61. Samarasinghe SNS, Woods C, Miras AD, et al. Bariatric Surgery in Women with Polycystic Ovary Syndrome. Metabolism. 2024; 151, 155745, ISSN 0026-0495
62. Bhandari M, Kosta S, Bhandari M, et al. Effects of bariatric surgery on people with obesity and polycystic ovary syndrome: A large single-center study from India. Obesity surgery 2022; 32:3305–12.

FOGSI 360
Coordinate Communicate Community
जीवनस्य वृत्तम्

FOGSI FOCUS
PCOS
PRACTICE POINTS
Algorithms for Obs & Gynae.