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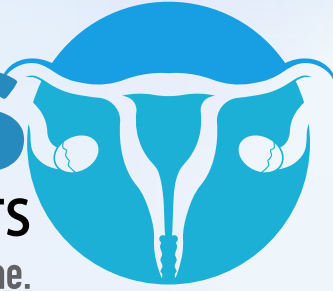
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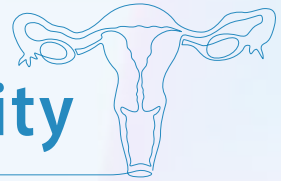
PCOS

PRACTICE POINTS

Algorithms for Obs & Gynae.



PCOS and Infertility



MANAGEMENT OF PCOS IN INFERTILE WOMEN (FOCUS ON NEWER MOLECULES & THERAPIES) PRACTICE POINTS

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Practice points

Management of PCOS in infertile women (Focus on newer molecules and therapies)

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Abstract

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 10-13% of women of reproductive age, contributing to approximately 70% of anovulatory infertility cases. PCOS is associated with various health risks, including metabolic syndrome, diabetes, cardiovascular disease, and psychological issues, such as depression and anxiety. Central to its pathophysiology are insulin resistance (IR) and hyperandrogenism, which exacerbate ovarian dysfunction, leading to infertility. Obesity, physical inactivity, and family history further increase the risk of PCOS.

Given its widespread impact on women's health, particularly reproductive health, this expert consensus aims to provide a validated, evidence-based approach to the treatment of PCOS and related infertility. The task force reviewed the existing literature and utilized their clinical expertise to develop key practice points, following a structured grading system for evidence appraisal. The recommendations are categorized by levels of evidence and classes of recommendations. Key practice points include: Lifestyle intervention involving exercise, diet, and behavioral strategies should be universally recommended to improve metabolic health and quality of life. Letrozole is the first-line pharmacological treatment for infertility in women with PCOS, followed by clomiphene with metformin, gonadotropins, or ovarian drilling as second-line options. In vitro fertilization (IVF) is a third-line treatment when ovulation induction therapies fail and metformin and myoinositol have demonstrated efficacy in improving clinical and cumulative pregnancy rates. This consensus highlights the importance of tailored treatments to optimize reproductive and metabolic outcomes in women with PCOS.

Keywords: Polycystic ovary syndrome; insulin resistance; management; In vitro fertilization

Introduction

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder in women of reproductive age that affects approximately 10-13% of women

of reproductive age.^{1,2,3} Ovulation disorders cause infertility in approximately 25% of couples, with PCOS being the main cause of anovulatory infertility, accounting for about 70% of all cases.⁴ PCOS can also result in long-term health

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complications including metabolic syndrome, diabetes mellitus, dyslipidemia, cardiovascular disease and endometrial cancer.⁵ Major risk factors that increase the likelihood of developing PCOS include obesity, lack of physical activity, family history, and environmental toxicity.¹ General & central obesity, menstrual irregularities, infertility, acanthosis nigricans, hirsutism, and acne are the signs and symptoms of PCOS.^{2,6,7} Additionally, PCOS has been shown to cause psychological stress, resulting in mood swings, low self-esteem, depression, and anxiety. Thus, PCOS significantly affects women's psychological health and quality of life.¹

Insulin resistance (IR), described as a metabolic condition leading to altered cellular responsiveness & impaired insulin signaling appears to be a fundamental pathophysiological mechanism in PCOS.⁸ Furthermore, compelling evidence indicates that hyperandrogenism may be a causative factor in the development of this condition.⁹

The cyclical pathogenetic interaction between IR, hyperinsulinemia, and hyperandrogenism, combined with hypothalamic-pituitary dysfunction, causes further ovarian dysfunction, potentially resulting in anovulation and infertility.⁴

Scope

The aim of this key practice points is to develop a validated treatment approach for PCOS and infertility.

Methodology

The task force reviewed the available literature and developed the consensus statement based on published literature, their individual clinical experience and focused discussion among the members. The task force members followed a well-defined grading system (Table 1) for the critical appraisal of evidence and grading strength of consensus.

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.

Management of PCOS related infertility

Lifestyle modifications

Recommendations as per guidelines

The international evidence-based guideline for the assessment and management of PCOS 2023 recommends lifestyle intervention— whether through exercise alone or a combination of diet, exercise, and behavioral strategies— for all women with PCOS, helps to improve metabolic health, including reducing central adiposity and enhancing the lipid profile. There is no evidence to support any specific diet composition or any type and intensity of exercise being better than another for improving anthropometric, metabolic, hormonal, reproductive, or psychological outcomes in women with PCOS.³

Ovulation induction

Ovulation induction is the mainstay for the treatment of PCOS women with infertility. Letrozole, clomiphene citrate (CC), gonadotropins, and metformin alone or in combination with the foresaid drugs are the most commonly used medications for ovulation induction.⁴

1. Letrozole

Letrozole is the most commonly used selective non-steroidal third-generation aromatase inhibitor (AI) for ovulation induction in PCOS. It works by inhibiting the secretion of ovarian estradiol.¹⁰ The latest evidence-based guidelines recommend letrozole as the first-line pharmacological treatment for ovulation induction in anovulatory women with PCOS who have no other infertility factors. Letrozole should be preferred over CC for women with PCOS who have anovulatory infertility and no other infertility factors, as it has shown to improve ovulation, clinical pregnancy, and live birth rates. Letrozole is also associated with reduced incidence of multiple pregnancy and miscarriage. Letrozole has the potential to reduce multiple gestation pregnancy and OHSS.¹¹ Current evidence shows comparable fetal abnormality rates between letrozole or CC among ovulation induction.³

2. Clomiphene citrate

Clomiphene citrate (CC), a selective estrogen receptor modulator (SERM), has been considered the first-line treatment for ovulation induction in women with PCOS for many years.⁴ According to current evidence-based guidelines³

- Clomiphene citrate may be preferred over metformin in women with PCOS who have anovulatory infertility and no other infertility factors in order to improve ovulation, clinical pregnancy, and live birth rates.
- The use of CC, whether alone or combined with metformin, increases the risk of multiple pregnancies. Therefore, clomiphene cycles may necessitate ultrasound monitoring.
- The combination of CC with metformin could be used over CC or metformin alone for improving ovulation and clinical pregnancy rates in women with PCOS with anovulatory infertility and no other infertility factors.

3. Gonadotropins

Evidence-based guidelines recommend that gonadotrophins can be used as a second-line pharmacological treatment for women with PCOS who are anovulatory and infertile, have no other infertility factors, and have failed first-line oral ovulation induction treatments.³ The use of gonadotropins in women with PCOS is associated with a higher risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. Therefore, these medications should only be administered by clinicians with the appropriate training and experience. Various gonadotropin preparations, such as follicle-stimulating hormone (FSH) and human menopausal gonadotropin, seem to be equally effective, with no significant difference in live birth rates, clinical pregnancy rates, multiple pregnancy rates, miscarriage rates, or the incidence of OHSS.⁴

Insulin sensitizing agents

1. Metformin

Metformin, an oral insulin-sensitizing agent, works by inhibiting hepatic glucose production, decreasing intestinal glucose uptake, and increasing insulin sensitivity in peripheral tissues. Metformin aids in improving ovulation induction in women with PCOS by lowering insulin levels and modifying the effect of insulin on ovarian androgen biosynthesis, theca cell proliferation, and endometrial growth. Metformin can be used alone or as an adjunct to other ovulation induction agents in women with PCOS who have no other infertility factors.¹²

Evidence-based guidelines recommend that metformin can be used alone to improve clinical pregnancy and live birth rates in women with PCOS who have anovulatory infertility and no other infertility factors, but patients should be informed that there are more effective ovulation induction agents. In women with PCOS experiencing

anovulatory infertility and no other infertility factors, combining CC with metformin could be used rather than metformin alone in improving live birth rates. Healthcare professionals should be aware that in pregnant women with PCOS, metformin has not been proven to prevent conditions like gestational diabetes, late miscarriage (between 12 weeks + 1 day and 21 weeks + 6 days gestational age), hypertension in pregnancy, preeclampsia, and macrosomia or birthweight ≥ 4000 g. In certain situations, such as when there is a risk of preterm birth, metformin could be considered in pregnant women with PCOS to help reduce the preterm delivery and limit excess gestational weight gain.³

2. Inositol

Inositols are used as therapeutic agents in women with PCOS due to their beneficial effects on follicular development, hormonal regulation, and glucose homeostasis. Numerous studies have shown the positive effects of inositol on metabolic, hormonal, and reproductive disturbances in PCOS, alone or in combination with other substances, increasing their therapeutic effect and bioavailability.¹³ Myoinositol (MI) decreases androgen levels (testosterone and androstenedione), balances the luteinizing hormone (LH)/FSH ratio, regulates menstrual cycles, and promotes ovulation, thereby facilitating spontaneous pregnancies by adequate progesterone production during the luteal phase.¹⁴

A randomized controlled trial in 2022 compared MI with Metformin in PCOS women undergoing in vitro fertilization (IVF). They found that clinical pregnancy rate & cumulative pregnancy rates were significantly higher in group who received MI 2 gm twice daily vs in group received Metformin 850 mg twice daily. They also reported that fertilization rate, cleavage rate & good grade embryo rate were also significantly higher in MI group than Metformin group.¹⁵

Inositol, in any form, may be considered in women

with PCOS according to individual preferences and values. It has minimal risk, and potential to improve metabolic parameters, but its clinical benefits, including effects on ovulation, hirsutism, and weight remain limited.¹⁶

Metformin + Myoinositol

Since the two insulin sensitizers, MI, and metformin, function via different mechanisms, combining them may yield synergistic effects, improving metabolic and reproductive outcomes in infertile PCOS women.¹⁷

A comparative study assessed the efficacy of metformin plus MI over metformin alone in 120 infertile women with PCOS undergoing ovulation induction. A significant improvement was observed in menstrual cycles (cycle length and bleeding days) in the group that received Metformin (500 mg) combined with MI (600 mg) three times daily than in group that received only Metformin (500 mg) three times daily. The improvement in HOMA-IR was also significantly greater in the combination group than in metformin group after 3 months. Additionally, the live birth rate was also significantly higher with combination therapy. The study concluded that women receiving the combination treatment had a significantly higher live birth rate compared to those treated with Metformin alone.¹⁷

A comparative study assessed the efficacy of MI over Metformin in 90 women with PCOS and vitamin D deficiency. They were classified into three groups of 30 women each: Group A (Metformin 500 mg three times daily), Group B (MI 2 gm twice daily) and Group C (Metformin 500 mg twice daily and MI 2 gm twice daily). At the end of treatment, 26.6%, 50% and 80% of women in groups A, B, and C, respectively had regular menstrual cycles. After 6 months of treatment, a reduction in polycystic ovaries was observed in 50% in group A, 80% in Group B, and 93.33% in Group C. Significant improvements were

noted in all three groups after 24 weeks, including reductions in acne, hirsutism, body mass index (BMI), serum LH, FSH, LH/FSH ratio, free testosterone, total testosterone, serum insulin levels, and total cholesterol levels, with higher significance observed in Group C. Therefore, when added to Metformin, MI can help normalize dysregulated metabolism in various tissues, including the ovaries, pancreas, and muscles, and enhance the effectiveness of Metformin to improve the clinical and biochemical features of PCOS.¹⁸

Furthermore, a prospective observational study compared the combined effect of Metformin and MI with Metformin alone in infertile women with PCOS undergoing ovulation induction cycles. A total of sixty patients participated in the study and were divided into two groups, Group A (n=30) received a combination of MI 600 mg and Metformin 500 mg three times daily, while Group B (n=30) received only MI 600 mg three times daily. Following six ovulation cycles, Group A exhibited a significantly higher clinical pregnancy rate than Group B. At 6 months, Group A achieved a total clinical pregnancy rate of 43.33%, whereas Group B received a rate of 26.67%, and the difference was statistically significant ($p < 0.01$). Both groups exhibited similar reductions in hormonal levels and improvements in clinical and laboratory parameters. However, the group receiving the combination of MI with Metformin demonstrated superior clinical fertility rates compared to Metformin alone.¹⁹

Laparoscopic ovarian drilling

Recommendations from guidelines

For women with PCOS and anovulatory infertility, laparoscopic ovarian surgery could be the second-line treatment, particularly for those resistant to CC, failure to oral ovulogens and no other infertility factors. When considering laparoscopic ovarian surgery for ovulation induction, several factors should be considered:³

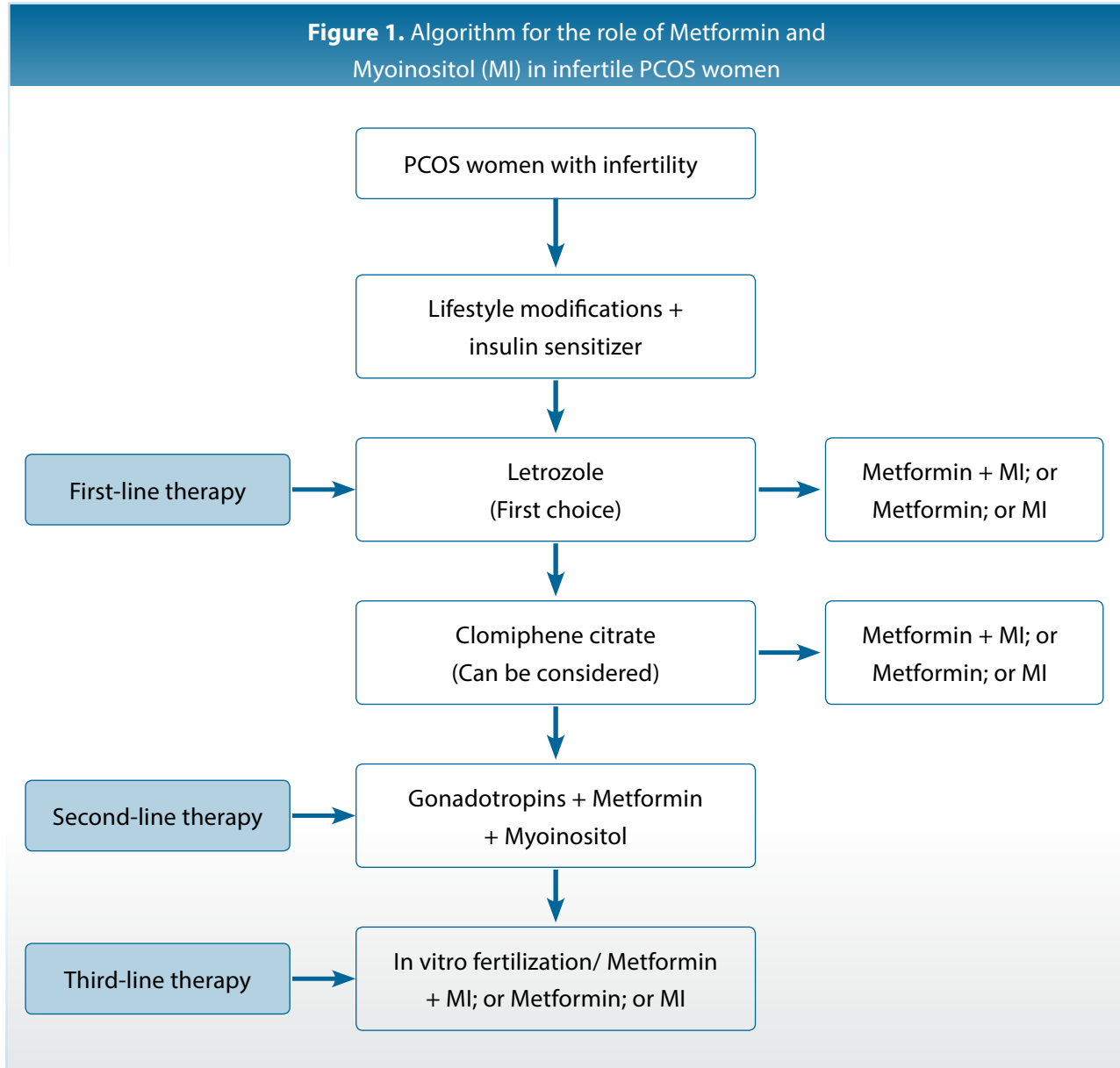
1. Cost comparison with other ovulation induction interventions.
2. The level of expertise necessary for safe implementation.
3. Both intraoperative and postoperative risks, like ovarian adhesions and diminished ovarian reserve.

Assisted reproductive technologies

In vitro fertilization (IVF), potentially with in vitro maturation, may be considered as a third-line therapy option for women with PCOS and anovulatory infertility when other pharmacological ovulation induction therapies have failed.³ While IVF is a highly effective treatment with pregnancy rates reaching up to 50% from a single treatment cycle, particularly in young women with a favorable ovarian reserve. IVF is associated with increased risk of OHSS but can be prevented by using GnRh agonist as trigger and freeze-all strategy.¹²

Algorithm for the role of Metformin and Myoinositol in infertile PCOS women

Figure 1. Algorithm for the role of Metformin and Myoinositol (MI) in infertile PCOS women



Practice points

- Lifestyle intervention, including exercise alone or combined with diet and behavioral strategies, should be recommended for all women with PCOS to improve metabolic health, and enhance quality of life (Level A/ Class I).
- Letrozole is the recommended first-line pharmacological treatment for infertility in women with PCOS, followed by CC in combination with metformin or gonadotrophins or ovarian drilling as the second-line treatment options. (Level A/Class I).
- In vitro fertilization (IVF), possibly with in vitro maturation, may be considered as a third-line treatment when other ovulation induction treatments have been proven to be ineffective (Level A/Class I)
- The combination of Metformin and Myoinositol demonstrates efficacy in improving clinical pregnancy rates and cumulative pregnancy rates in women with PCOS (Level A/ Class IIa).

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