Clinical Practice Guideline

Good clinical practice recommendations on management of infertility in patients from India with polycystic ovary syndrome

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INTRODUCTION AND RATIONALE

Polycystic ovarian syndrome (PCOS) is a principal endocrine system disorder affecting women of reproductive age. The cardinal features of PCOS are androgen excess (AE), chronic anovulation, and the presence of polycystic ovarian morphology.[1] Further, insulin resistance (IR), increased gonadotropin-releasing hormone (GnRH) drive, and a proclivity for weight gain are observed in women with PCOS.[2,3]

Hyperandrogenemia mediates ovarian alterations and increases pituitary luteinizing hormone (LH), pulse frequency, and amplitude with resultant relatively low follicle stimulating hormone (FSH) secretion. Hence, most women with PCOS are characterized by an elevated LH/FSH ratio. LH hypersecretion in PCOS is probably owing to enhanced pituitary sensitivity to GnRH or to changes in GnRH secretion patterns rather than increased GnRH secretion. In addition, obesity is a comorbidity that may amplify the effects of PCOS and compensatory hyperinsulinemia may actually stimulate hyperandrogen production in the adrenal gland and ovary in PCOS.

Collectively, all of the above factors contribute to impaired folliculogenesis and resulting anovulation. About 85–90% of women with oligomenorrhea and 30–40% of women with amenorrhea present with PCOS.[4] The data extrapolated from World Health Organization (WHO) by the Indian Council of Medical Research suggest that approximately 13–19 million couples are likely to be infertile in India at any given time, and approximately 50% of the patients attending fertility clinics in India are diagnosed with PCOS.[5-7] Moreover, the treatment of infertile women with PCOS is surrounded by many controversies and the incidence of ovarian hyperstimulation syndrome (OHSS) is high with ovulation induction (OI) in these women. Further, the risk of multiple pregnancies and pregnancy loss in the first trimester affect the overall pregnancy rate in women with PCOS. The risk of pregnancy complications, such as pre-eclampsia (hypertension during pregnancy) and gestational diabetes, is also increased in PCOS.

Despite a marked development in the area of infertility management in India including in those with anovulatory PCOS, many patients do not receive structured medical

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care based on the best available evidence as a result of lack of uniform practices in a clinical setting. Therefore, the present guideline will direct optimal medical and surgical management of infertility associated with PCOS in Indian women. It also covers recommendations on areas of counseling required for infertile couples where the woman suffers anovulatory PCOS.

METHODOLOGY

The current Good Clinical Practice Recommendations (GCPR) by the Indian Fertility Society for the management of infertility in women with PCOS were developed by an "expert panel" of obstetricians, gyneco logists, and endocrinologists from across the country with vast experience in managing patients, especially PCOS patients with infertility.

A group of panel members reviewed the literature and collected the evidence. A literature search was performed electronically in the medical search engine "PubMed" and "Google Scholar" for relevant studies. The main search strategy included the following keywords: polycystic ovary syndrome, PCOS, OI, and infertility with no limitation of time. Further, the section headers in the current document were used as keywords along with the main keywords. Specific evidence from India was identified using "India" as the keyword wherever appropriate. In addition, a manual search was made from key nonindexed journals. Only abstracts written in English were included. Evidence from randomized clinical trials (RCTs) and non-RCTs conducted in India and abroad were considered for framing the GCPR. However, evidence from RCTs, non-RCTs, and retrospective and uncontrolled studies were thoroughly reviewed, as well as reviews and meta-analyses were handpicked for contemplation. Existing recommendations from national and international guidelines for the management of infertility in PCOS were keenly observed for the areas with little evidence.

The draft guideline, with proposed GCPR for the manage ment of infertility in PCOS in Indian women, was reviewed by the "expert panel" members through mail communications followed by a physical meeting. During the physical meeting, a series of discussions were made to arrive at a consensus on each GCPR for the management of infertility in PCOS in Indian women. In areas where evidence was weak or did not exist, the consensus opinion of the expert panel had been relied upon. Grading of recommendations followed the American Association of Clinical Endocrinologists (AACE) guidelines [Table 1].[8]

Table 1: Grading of recommendations

Strength of recommendation
A Strongly recommended
B Suggested
C Unresolved
Scale of scientific support
1 At least one RCT or meta-analysis of RCTs
2 At least one non-randomized/non-controlled, prospective epidemiological study
3 Cross-sectional or observational or surveillance or pilot study
4 Existing guideline or consensus expert opinion on extensive patient experience or review

DIAGNOSIS OF INFERTILITY IN PCOS

In PCOS, there is an interplay between the perpetually elevated levels of androgens (both locally and peripherally), insulin sensitivity, and the hypothalamic–pituitary axis. Accordingly, a typical assessment for a patient presenting with infertility and irregular periods or ovulation includes focus on history and physical examination with investigation for elements of PCOS and different etiologies for anovulation. Hyperandrogenism and ovulatory dysfunction are the principal clinical manifestations of PCOS. The tests for diagnosis and confirmation of PCOS and exclusion of symptomatic disorders in the Indian context have been recently brought forward by the Indian Fertility Society.[1] According to WHO, anovulatory dysfunction is classified into three broad categories based on the levels of serum gonadotropins, i.e., FSH, LH, and estradiol. Differentiating the definite category of anovulation amidst the three is crucial in developing a treatment strategy. However, these sorts of anovulation are not totally unrelated, and in some cases, PCOS patients may likewise have modified or diminished release of gonadotropins (category 1) or ovarian senescence (category 3).[9]

Rotterdam criteria recommend assessment of the antral follicle count (AFC) on ultrasound as one of the diagnostic criteria for PCOS. These small antral follicles synthesize anti-Müllerian hormone (AMH). Serum AMH could, therefore, be used as a surrogate for AFC in the diagnosis of PCOS. There exists a good correlation between AMH and AFC.[10,11] AMH levels reflect the number of developing follicles and can be used as a marker of the ovarian reserve with promising prognostic potential in reproductive medicine and as a marker of ovarian follicle impairment in women with PCOS.[12] AMH measurement may guide as a marker during stimulation protocols, suggesting a possibility of OHSS. A cross-sectional study from India observed that baseline serum AMH levels were two-fold higher in infertile women with PCOS than healthy infertile women,[13] suggesting it as

a potential marker for recruited nongrowing follicles as well. Elevated AMH values (≥4.5 ng/mL) have been suggested as a substitute for ovarian morphology in the absence of accurate ovarian ultrasound.[14]

Existing guidelines

The recent guide to the best practices in the evaluation and treatment of POCS by AACE and American College of Endocrinology and AE Society recommends AMH testing in the diagnosis of PCOS.[14]

Recommendations on diagnosis

The recommended diagnostic workup in subfertile women with PCOS includes the following:

1. Clinical determination of two of the three Rotterdam criteria (including AFC) (Grade A, EL 4).
2. Biochemical determination of testosterone (Grade B, EL 4), AMH (Grade B, EL 4), and 17-hydroxyprogesterone in women with hirsutism and negative progesterone withdrawal bleed (Grade B, EL 4).

MANAGEMENT OF INFERTILITY IN WOMEN WITH PCOS

In women with anovulatory PCOS seeking restoration of fertility and achieving singleton live birth, OI should be the primary aim. The mechanism of OI is based on the physiologic concept that initiation and maintenance of follicle growth are achieved at physiologic levels of FSH to generate a sufficient number of mature follicles. Because women with PCOS are prone to excessive multiple follicle development, it is essential to aim at achieving OI for successful clinical pregnancy.

The strategies for the management of infertility in anovulatory PCOS include the following:

1. Preconceptional counseling,
2. Lifestyle modifications,
3. Pharmacological interventions,
4. Surgical management, and
5. Assisted reproductive technologies.

PATIENT COUNSELING: PRIOR TO AND DURING THE TREATMENT

In women with PCOS, the symptoms may be associated with the incidence of depression, anxiety, perception of loss of feminine identity, and sexual dysfunctions, and may trigger social isolation, compromising the quality of life (QoL).[15] It is essential for the healthcare professionals to provide counseling on the physiological and emotional well being of the woman with PCOS. It is of utmost importance for the healthcare professionals to spend sufficient time with the couple seeking fertility, explain in detail the various procedures involved with anovulatory PCOS women, and address their queries. This will build rapport and trust, and help the couple plan other priorities in their lives (career or family commitments). Moreover, counseling informs them about the course of treatment and justifies their right of being informed.

The counseling before treatment initiation or during the course of treatment could include but was limited to the following general areas:

1. Identify risk factors and rectify them before treatment initiation (cease smoking or usage of smokeless tobacco and limit alcohol consumption).
2. Advice/educate on behavioral change, motivational interviewing, and chances of pregnancy.
3. Multivitamin, vitamin D, vitamin B_{12}, folate, iron, and calcium supplementation.
4. Length of procedure, types, side effects, success rate, cost, and husband's role.
5. Lifestyle: Achieving healthy weight (min. 5% weight loss) in obese (≥25 kg/m^2) women.
6. Face-to-face counseling on symptomatic improvement, tailored dietary advice in consultation with a dietician, and exercise using audio-visual means, charts, pamphlets, group activity sessions, etc.
7. During OI with clomiphene citrate (CC) and gonadotropin, counseling on risk of multiple pregnancy and OHSS.
8. Risk and benefit associated with laparoscopic ovarian drilling (LOD) and bariatric surgery.
9. Avoiding pregnancy for at least 12–18 months after bariatric surgery.

Existing guidelines

The European Society of Human Reproduction and Embryology (ESHRE) 2008 consensus statement suggests preconceptional counseling in women with PCOS on identifying and correcting risk factors for infertility, recognizing the presence of obesity and its distribution, and use of folate supplementation.[16] The Royal College of Obstetricians and Gynaecologists (RCOG) 2014 recommends informing patients about long-term risks of PCOS treatment.[17] The Australian PCOS-alliance 2010 recommends patient counseling regarding bariatric surgery, for avoiding pregnancy for at least 12–18 months after surgery, and taking care of risks of preoperative and postoperative nutritional deficiencies.[18]

Recommendations on patient counseling

1. PCOS women with subfertility should be counseled on the need for identification and correction of long-term risk factors affecting fertility before initiating treatment (Grade A, EL 4).
2. In PCOS women with subfertility, the healthcare professionals are recommended to provide pretreatment counseling on weight reduction using lifestyle modification and behavioral changes (Grade A, EL 4).
3. It is recommended that healthcare professionals emphasize the role of the husband in emotional well being of subfertile PCOS women during the course of treatment (Grade B, EL 4).
4. PCOS women with subfertility should be counseled on length of procedure, types, side effects, success rate, and cost of treatment (Grade B, EL 4).

LIFESTYLE MODIFICATIONS AND BARIATRIC SURGERY FOR WEIGHT REDUCTION

Lifestyle modification intended to reduce body weight and overcome IR is the first-line treatment in women with PCOS.

Current evidence

Obesity is defined as body mass index (BMI) ≥25 for Asian Indians.[19] Obesity is strongly associated with PCOS and may be present in up to 50% of the patients.[20-26] Obese women with PCOS are more likely to suffer from anovulation than thin women with PCOS.[27,28] Further, studies show that overweight women are less likely to respond to pharmacologic OI methods.[29-35] Obesity contributes to the poor obstetric outcome, increased risk of spontaneous abortion, and preterm labor, and increases maternal complications, thromboembolism, gestational diabetes mellitus, wound infection, and gestational hypertension.[36-38] Therefore, weight loss by lifestyle modification (and/or pharmacological therapy) is the primary treatment for PCOS women before infertility management. Once patients have achieved weight loss, they should be encouraged to maintain this in the long run and to have normal weight gain during pregnancy.

Treatment of obesity is multifaceted and involves behavioral counseling, lifestyle modification (hypocaloric diet and exercise), pharmacological treatment, and bariatric surgery.

1. *Diet and exercise*: Weight loss through exercise and diet restores ovulatory cycles and increases pregnancy rates. Gradual weight reduction is recommended so as to increase the chances of maintaining the weight loss. The diet composition for weight loss in PCOS women has been evaluated in two small studies. These studies compared a low carbohydrate (40%), high protein (30%) hypocaloric diet with a high carbohydrate (55%), low protein (15%) hypocaloric diet and reported similar reduction in weight, circulating androgen, and insulin levels. Although the patient sample size was small, these two studies suggest that patients can safely pursue either of the dietary compositions.[39,40] A recent systemic review of randomized trials on dietary composition in the treatment of PCOS concluded that to target weight loss in all overweight women with PCOS, reduction in caloric intake should be achieved with any diet (with adequate nutritional intake and healthy food choices), irrespective of composition, and it should meet nutritional requirements for women of reproductive age.[41] Regular physical activity is essential for reproductive health of women with PCOS. The studies in non-PCOS patients show that diet and/or exercise increases insulin sensitivity and helps achieve and maintain weight loss.[42-45] In an Indian evidence, 3 months of aerobic exercise reduced weight and increased ovulation and pregnancy rate in women with PCOS.[46]
2. *Diet and exercise along with pharmacological ovulation-induction agents*: A total of 10 RCTs compared various types of lifestyle interventions (including low carbohydrate or healthy diets with and without exercise programs) to pharmacological therapy (including metformin or CC) in women with PCOS and BMI ≥ 25 kg/m^2.[29,47-54] In the studies comparing lifestyle (diet) therapy (with or without placebo) to pharmacological therapy plus lifestyle (diet) therapy, the majority of them reported that there was no difference between the interventions in terms of OI and pregnancy rate.[47-52] Lifestyle management had higher pregnancy rate compared to CC alone or in combination with metformin.[53] The CC response was found to be improved with lifestyle modi- fications.[29,54] In a study by Palomba *et al.*,[29] structured exercise for 2 weeks followed by OI by CC with continuous exercise resulted in higher pregnancy rates in clomiphene citrate resistance (CCR) patients. In a study by Legro *et al.*,[54] the adverse metabolic effects of oral contraceptive pills (COCPs) were inhibited by lifestyle modification and had higher ovulation rate than COCPs only. Nevertheless, the live birth rate was greater with lifestyle modification only.
3. *Pharmacological weight-reducing agents*: In obese women with PCOS, antiobesity pharmacological agents have been used despite few quality studies.[55,56] Both orlistat, which blocks intestinal absorption of fat, and

sibutramine,[56-60] an appetite suppressant, have displayed weight loss resulting in an improvement in cardiovascular risk factors, hyperandrogenemia, and IR.[55,61-63] It should be noted that these treatments should not be considered as first-line therapy for weight reduction in obese women with PCOS.

Kumar and Arora[64] from India have shown greater weight reduction compared to lifestyle intervention alone. In this study, women with PCOS were randomized to receive either of the two drugs (orlistat or metformin) in combination with lifestyle interventions or lifestyle interventions alone. Orlistat and metformin were found equally effective in reducing weight and accomplished comparative ovulation rates in obese PCOS patients. However, orlistat had minimal side effects and was better tolerated compared with metformin.

4. *Yoga as an aid to treatment*: Yoga and meditation are considered as holistic approaches for treating the root cause of PCOS (obesity and stress). Studies conducted by comparing yoga to the conventional physical exercises in three randomized trials for the duration of 1 h per day for 12 weeks in women with PCOS revealed, significant improvement in glucose, lipid profile, IR values ($P < 0.05$), and anxiety ($P = 0.002$).[65-67] Significant reduction of AMH ($P = 0.006$), LH ($P = 0.005$), LH/FSH ratio ($P = 0.015$), testosterone ($P = 0.014$), modified Ferriman and Gallwey score (mFG) ($P = 0.002$) for hirsutism, and an improvement in menstrual frequency ($P = 0.049$) were obtained in a similar study.[68] Regular practice of various yoga postures helps in weight loss and increases ovarian blood supply, thereby assisting in management of PCOS; hatha yoga is used as a psychological adjuvant in women undergoing *in vitro* fertilization (IVF).[69,70] Further, Kadam *et al.*[71] recommended different yoga asanas beneficial in women with PCOS.

   It is important to note that there was inconsistency in the components of lifestyle therapy and therefore a recommendation cannot be made about a specific intervention; however, given that there is no difference between lifestyle and pharmacological therapy overall, the clear benefits in using lifestyle interventions over pharmacological interventions can be recommended. It is also recommended that these interventions should be conducted prior to pregnancy, not concurrently with infertility treatment, until the risk–benefits of these therapies on pregnancy are better understood.

Existing guidelines

Australian PCOS-alliance 2010 and the Society of Obstetricians and Gynaecologists of Canada (SOGC) 2010 recommend lifestyle management, including diet and exercise programs, as first-line therapy for 3–6 months, not in combination with pharmacological OI.[18,72] Moreover, Australian PCOS-alliance 2010 recommends against pharmacological OI until appropriate weight loss has occurred through diet, exercise, bariatric surgery, or other appropriate means in women with BMI ≥ 35 kg/m^2. Similar lifestyle modifications are recommended by RCOG 2014,[17] but with preceding and/or accompanying pharmacological treatment. ESHRE 2008 recommends any hypocaloric diet (with a 500 kcal/day deficit) with reduced glycemic load with which patients can comply and achieve a 5% weight loss.[16]

Recommendations on lifestyle intervention for management of subfertility in PCOS

1. Lifestyle modifications targeted at weight reduction (at least 5%) or prevention of weight gain are recommended as first-line therapy before attempting pharmacological methods of OI in subfertile women with PCOS (Grade A, EL 1).
2. Lifestyle modification should include calorie restriction with any hypocaloric diet (reduced by 500 kcal/day) and physical activity of 60 min/day up to 3 months along with restriction of other risk factors (excessive caffeine intake, alcohol consumption, and smoking) (Grade A, EL 2).
3. The age-related decline in fertility should be given appropriate consideration for considering the duration of lifestyle management interventions (Grade B, EL 4).
4. In PCOS patients with subfertility who are morbidly obese (BMI > 35 kg/m^2), pharmacological methods of OI should be avoided before weight reduction (Grade B, EL 4).
5. Yoga is recommended as a part of lifestyle management workup as an aid for the treatment of subfertile PCOS women (Grade B, EL 3).
6. The treatment with orlistat is recommended under medical supervision in an event of unsuccessful weight reduction with diet and exercise alone for 2–3 months in morbidly obese patients (Grade B, EL 1).

BARIATRIC SURGERY

Bariatric surgery can be an effective means of not only weight loss, but also an improvement of other PCOS conditions such as anovulation, metabolic syndrome, and hyperandrogenism in PCOS women with morbid obesity (BMI ≥ 35 kg/m^2).

Current evidence

The following three bariatric surgery procedures are performed commonly: laparoscopic adjustable gastric

banding (LAGB), laparoscopic sleeve gastrectomy (LSG), and laparoscopic roux-en-Y gastric bypass (LRYGB).[73] Evidence on the role of bariatric surgery as a successful management strategy in PCOS women of reproductive age with morbid obesity is limited. However, among the three, LAGB and LRYGB have shown promising results in weight reduction, improvement in menstrual cycles, and reproductive benefits in women with PCOS.[74,75] Bariatric surgery is known to improve menstrual cyclicity in anovulatory women, but there is a scarcity of published data on the influence of surgical weight loss on spontaneous or IVF pregnancy rates. In a prospective study, bariatric surgery, with mean weight loss of 41 kg, ameliorated androgen profiles and IR index (HOMA-IR) in 50% of the patients, which produced a correction of menstrual function (12/17) and spontaneous ovulation (10/12).[74] In another retrospective review in PCOS women with LRYGB, improvement in menstruation and spontaneous pregnancy after surgery was demonstrated when followed up for >2 years.[75]

Bariatric methods can result in malabsorptive states, poor food tolerance, or psychological issues, which may compromise nutritional status, particularly with ongoing vomiting and or disordered eating, and may contribute to a greater nutritional risk that may impact adversely on fertility, and maternal and neonatal complications. Women may be at particular risk of deficiencies in iron, folate, and iodine in addition to other nutrients as the recommended daily intake increases in pregnancy. Although supplements are commonly recommended following bariatric surgery, there are reports of poor compliance to supplement use in pregnant women with only 10% taking adequate folate.[76,77] Patients are required to be counseled on these aspects of surgery.

Currently, there is no documented evidence from India on the use of bariatric surgery as a means of weight reduction in PCOS women with infertility.

Existing guidelines

According to the most recent clinical guidelines for obesity management in the general population, obesity surgery can be considered (1) after nonsurgical treatment has been attempted unsuccessfully for at least 6–12 months in adults with a BMI $\geq 35\ kg/m^2$ and (2) it can be first-line treatment instead of lifestyle interventions or drug treatment in adults with BMI $\geq 50\ kg/m^2$. The guidelines also come to an agreement on insufficient evidence for recommending bariatric surgery with a BMI $\leq 35\ kg/m^2$.[78] ESHRE 2008 and RCOG 2014 recommend bariatric surgery for morbidly obese women with PCOS (BMI of $\geq 40\ kg/m^2$ or $\geq 35\ kg/m^2$ with a high-risk obesity-related condition) if standard weight loss strategies have failed.[16,17] On the other hand, Australian PCOS-alliance 2010 guideline recommends bariatric surgery as second-line therapy in adult women with PCOS (anovulatory, BMI $\geq 35\ kg/m^2$) and who remain infertile despite undertaking an intensive (frequent multidisciplinary contact) structured lifestyle management program to improve fertility outcomes.[18] They recommend counseling on the following areas:

1. Postsurgery weight loss interventions and efforts to improve psychological, musculoskeletal, and cardiov ascular health should be continued.
2. The patient should be informed about the risk of preoperative and postoperative nutritional deficiencies.
3. Pregnancy should be avoided during periods of rapid weight loss. Patients should be counseled to avoid pregnancy for at least 12–18 months after bariatric surgery, and if pregnancy occurs, the patient should be made aware of the risk of preoperative and postoperative nutritional deficiencies. Fetal growth should be monitored during pregnancy.

Recommendations on use of bariatric surgery

1. Bariatric surgery is recommended as second-line treatment in morbidly obese (BMI $> 30\ kg/m^2$), subfertile PCOS patients who are unsuccessful in achieving weight reduction by lifestyle modifications (Grade B, EL 4).
2. In PCOS patients with BMI $> 50\ kg/m^2$, bariatric surgery is suggested as first-line therapy for weight reduction (Grade B, EL 4).
3. It is recommended to avoid conception for at least 12 months after bariatric surgery in PCOS women with subfertility because the effects of these interventions on the evolution of early pregnancy are not yet known (Grade B, EL4).

PHARMACOLOGICAL INTERVENTION

Pretreatment with combined oral contraceptive pills

Combined oral contraceptive pills (COCPs) reduce hyperandrogenism by promoting direct negative feedback on LH secretion, which results in decreased ovarian synthesis of androgens, and thereby normalize the LH/FSH ratio. Once the physiologic LH and FSH levels are reached, the FSH levels can be gradually increased for OI. Usually, <50 μg of estrogen (15–35 μg ethinylestradiol) in combination with progestin (with low androgen effects) are available as low-dose COCPs. Serum LH, FSH levels, LH/FSH ratio, and estrogen concentrations have to be monitored.

Current evidence

In a prospective, nonrandomized, observational study, pretreatment for 2 months with COCPs, followed by repeat CC 100 mg, in anovulatory women with resistance to CC has shown 72.6% ovulatory cycles with a cumulative pregnancy rate of 58%. Similarly, RCT conducted in women with PCOS ($N = 85$) undergoing in vitro fertilization embryo transfer (IVF-ET), pretreatment with COCPs remarkably increased the duration of gonadotropin stimulation and consumption ($P < 0.01$), significantly reduced the formation of ovarian cyst ($P < 0.05$), and markedly raised the percentage of mature ova (87.92 vs. 92.85%, $P < 0.05$).[79] However, the rates of fertilization, miscarriage, and clinical pregnancy, incidences of moderate and severe OHSS, and the number of retrieved oocytes were similar between the groups. The pretreatment with COCP favorably altered free androgen index when followed over 24 months in patients with PCOS in a randomized trial.[80] Similarly, in another randomized trial, comparing two different regimens of COCPs, both regimens had quite similar efficacy on hyperandrogenism after three cycles of therapy and without any changes in metabolic parameters.[81]

A line of evidence from India also shows beneficial effects of COCP in PCOS patients. There are two Indian studies on the use of COCP. In a prospective, nonrandomized study in anovulatory women (73.9% PCOS patients) with CC resistance, administration of monophasic low-dose COCP (0.03 mg ethinyl estradiol and 0.15 mg desogestrel) for two cycles followed by repeat CC (100 mg/day) for 5 days demonstrated successful OI. Folliculogenesis monitored using transvaginal ultrasound (TV-USG) from day 10 of the cycle (repeated every day) revealed lead follicle (mean diameter >20 mm) in the first (16.1% women) or second cycle with CC.[82] Further, an RCT on women with PCOS treated with a combination of metformin plus COCP or the individual drugs reported significantly better regularization of the menstrual cycle with the combination than monotherapy of either drug.[83] In a randomized trial comparing two contraceptive pills, containing drospirenone and 20 μg or 30 μg ethinyl estradiol, the decrease in free androgen index from baseline was 5.23 ± 5.79 with 30 μg and 4.99 ± 5.86 with 20 μg ($P = 0.82$).[84]

Existing guidelines

The existing guidelines do not comment on COCP pretreatment in PCOS women with subfertility.

Recommendations on pretreatment with COCP

1. Low-dose combined COCPs pretreatment (with or without lifestyle modifications) for at least 2 months is recommended in subfertile PCOS patients with high LH level (three times the basal levels) to normalize it (Grade B, EL 4).

Clomiphene citrate

Current evidence

CC is a selective estrogen receptor modulator with both estrogenic and antiestrogenic properties. It has been used for over 40 years. Acting as an antiestrogen, CC competitively inhibits the binding of estradiol to estrogen receptors in the pituitary and hypothalamus, which in turn blocks the negative feedback effect of endogenous estrogens. This release of hypothalamus from negative inhibition results in an increased secretion of pulsatile GnRH secretion from the hypothalamus with a subsequent increase in FSH and LH production and secretion from the pituitary gland. Consecutively, stimulating follicular growth leads to a midcycle LH surge and then ovulation.[85,86] Food and Drug Administration (FDA)-approved initial dosage is 50 mg daily for 5 days per cycle on menstrual cycle day 2–5. If patients do not ovulate at a dose of 50 mg, it may be increased up to 100 mg daily. Ovulation is expected 5–10 days after the last dose of CC. The dosages higher than 100 mg daily are not recommended by the manufacturer; however, increments up to 150 mg are used by some clinicians taking into account the cost and risk associated with the gonadotropin, which are the alternatives to CC.[72] If ovulation cannot be achieved with CC administration at doses of 150 mg/day for three cycles, CC resistance is reached.[87,88] Treatment generally should be limited to six (ovulatory) cycles.[89,90] In the event that pregnancy cannot be accomplished after six ovulatory cycles with CC, the patient is described as having CC conception failure.[91] When the patient does not ovulate even at CC dosage of 150 mg daily, an alternative to CC should be considered, because the administration of higher than 150 mg daily for 5 days does not further increase ovulation rate.[31] Moreover, additional cycles (maximum 12 in total for a lifetime of the patient, as explained later) may be considered on an individual basis after discussion with the patient.

Studies with CC have shown an ovulation rate of 60–85% and a pregnancy rate of 30–50% after six cumulative CC cycles.[90,92] Lower pregnancy rates despite good ovulation rates might be due to the antiestrogenic effects of CC on the endometrium and cervical mucus. However, in women with persistently thin endometrium, alternatives to CC should be considered. Approximately 50% of the conceptions will occur on 50 mg, with another 20–25% and 10% occurring on 100 mg and 150 mg, respectively.[90,92] TV-USG can be used for assessment of follicular development and endometrium, or by detection of the preovulatory LH surge with urinary kits.[93]

Prediction models have been developed to estimate the probability of ovulation by CC. Free androgen index was found to be the best predictor in univariate analysis.[31] The predictors of conception rate were age and cycle history (oligomenorrhea vs. amenorrhea), identified by multivariate analysis.[32] The main factors that predict live birth are obesity, hyperandrogenemia, and age.[94] Ovarian volume and menstrual status are additional factors that help to predict live birth with CC.[89]

Increased rate of multiple pregnancy and side effects such as vasomotor hot flashes are the major concerns with the use of CC. Further, unusual visual symptoms are reported in 1–2% PCOS patients taking CC with OI, probably due to antiestrogenic effects of CC on the visual cortex.[95] Therefore, it might be adept to limit treatment cycles with CC to 12 during patient's lifetime since additional cycles may place the patient at increased risk of borderline ovarian tumors.[96,97] The incidence of OHSS is less than 1%.[98]

A systematic review of randomized trials found that CC was better than placebo for pregnancy rate per patient and ovulation rate per patient in women with PCOS, including those whose sensitivity to CC was not reported. The evidence obtained from this systematic review is generalizable to the patient population in terms of age and BMI.[87] A recent survey on the knowledge, attitude, and practice of gynecologists ($N = 771$) across India, on the usage of CC for OI, reported that majority of the gynecologists preferred CC for the treatment of ovulatory dysfunction with very good to excellent efficacy and safety in women with PCOS.[99] Data from an RCT comparing CC alone versus combination with bromocriptine in PCOS women with normal prolactin found similar OI and pregnancy outcomes in both treatment groups.[100] In a prospective observational study, tamoxifen, an off-label indication for OI, was found to be a good alternative in PCOS women intolerable to side effects of CC.[101]

Existing guidelines

CC remains the first-choice treatment for induction of ovulation in most anovulatory women with no other infertility factors with monitoring of multiple pregnancy risk. The starting dose of CC should be 50 mg/day (for 5 days) and the recommended maximum dose is 150 mg/day up to six cycles.[16-18,72,102]

Recommendations on clomiphene citrate

1. In anovulatory PCOS women with subfertility, CC is recommended as a first-line pharmacological agent at a starting dose of 50 mg/day starting from day 2 of the menstrual cycle for 5 days. The maximum recommended dose of CC for OI is 150 mg/day, and increased by 50 mg/day at each cycle for a maximum of six cycles (Grade A, EL 1).
2. Ultrasound monitoring should be offered to infertile PCOS women who are on CC for monitoring of ovulatory response and to minimize the risk of multiple pregnancy. In an event of unavailability of ultrasound, monitoring of LH levels can be another alternative (Grade B, EL 3).

Insulin-sensitizing agents

IR with compensatory hyperinsulinaemia is a prominent feature of PCOS affecting approximately 65–80% of women with PCOS.[103] The association of IR contributing to anovulation in PCOS in an attempt to restore ovulation and improve the chances of pregnancy has led to the introduction of insulin-sensitizing drugs. Though troglitazone was used in some trials involving women with PCOS, it was withdrawn from the market in March 2000 (FDA 2002) because of reported risk of liver toxicity. Rosiglitazone and pioglitazone are classified as pregnancy category C drug according to FDA because of the potential risk of causing fetal growth restriction in animal experiments.[104] A high incidence of weight gain among the users further hampers its use in obese women with PCOS.[105,106] There is also a concern of the link between rosiglitazone and increased risk of myocardial infarction.[107] Therefore, it is unlikely that thiazolidinediones would have a major role in treating women with PCOS.[108]

Of the insulin-sensitizing drugs, metformin has been the most widely studied drug in PCOS with the most reassuring safety profile.[109] A standard dose of metformin is not proposed in clinical practice; however, various studies on using different protocols suggested an extremely variable target dose of 1500–2550 mg/day.[110] Patients should be informed on unpleasant side effects such as nausea, bloating, cramps, and diarrhea, which are often experienced with metformin. A starting dose of 500 mg daily during the main meal for 1–2 weeks can lessen the side effects and allow development of tolerance. The dose can be increased by 500 mg/day weekly or biweekly if required, until a maximum dose of 2500–2550 mg/day. If side effects worsen with increased dose, the current dose is maintained for 2–4 weeks until tolerance is developed. Slow release metformin can be associated with fewer side effects.[111,112]

Current evidence

There is heterogeneity in the evidence about the efficacy of metformin for rates of ovulation, pregnancy, and live birth across the subgroups, including BMI ($\leq$ or $\geq$30 kg/

m^2) and sensitivity to CC. The evidence provides support for the use of CC over metformin (no advantage of adding metformin to standard therapy of CC in terms of ovulation, pregnancy, and live birth rate).[108,113-121] Therefore, metformin should be used (alone or in combination with CC) only in women with PCOS who have not responded to CC as first-line therapy either in terms of ovulation or pregnancy.[108,122-127] Metformin has been found to reduce the incidence of OHSS.[118]

In a controlled clinical trial in PCOS women with infertility ($N = 24$), metformin and CC combination resulted in a significantly higher rate of ovulation (70 vs. 39.4%, $P = 0.0016$) and pregnancy rate (25 vs. 8%, $P = 0.194$) compared to CC or metformin alone.[128] In another RCT, sequential treatment with metformin and CC was found to be effective and safe option for clomiphene-resistant women with PCOS.[129] Metformin treatment in women with PCOS has shown good menstrual cyclicity and fertility in prospective studies.[130-133] On the contrary, following the treatment with rosiglitazone and CC or LOD and CC, biochemical response, ovulation rate, and pregnancy rate were comparable.[134]

In women with PCOS, continuing the metformin treatment during the pregnancy has been a topic of research and practical importance. A randomized, controlled trial by Vanky *et al.*[135] in PCOS women demonstrated that continuing metformin treatment from the first trimester to delivery did not cause any reduction in pregnancy complications. However, some studies have shown that continuing metformin in pregnancy may decrease the spontaneous abortion rate although none of these was a prospective, randomized trial.[136-139]

Existing guidelines

The ESHRE guideline 2008 suggests restricting the use of metformin in patients with glucose intolerance. However, the Australian alliance 2011 recommends adding metformin to CC in CCR women with a BMI $\geq 30\ kg/m^2$ (obese), and who are infertile with no other infertility factors. The European Society of Endocrinology (ESE) recommends the use of metformin as an adjuvant therapy for infertility to prevent OHSS in women with PCOS undergoing IVF. SOGC and RCOG recommend metformin combined with CC in women with CCR who are older and have visceral obesity.[16-18,72,102]

Recommendations on insulin sensitizing agents

1. Metformin is recommended in the following circumstances:
   a) In PCOS patients with impaired glucose intolerance (disturbed oral glucose tolerance test).
   b) In obese PCOS women coadministered with clomiphene.
   c) In CC-resistant PCOS women.
   d) In PCOS women who are at high risk of hyperstimulation.
2. It is recommended to start with a dose of 500 mg daily during the main meal of the day for 1–2 weeks, followed by 500 mg/day weekly or biweekly if required, until a maximum dose of 2500–2550 mg/day is reached. If side effects worsen with increased dose, the current dose is maintained for 2–4 weeks until tolerance is developed.

Gonadotropins and GnRH analogs

Gonadotropin therapy is second-line therapy in anovulatory PCOS women with either CC resistance or failure to conceive.[16,18,72,102] Various gonadotropin preparations have been used, which include human menopausal gonadotropin (hMG), recombinant FSH (rFSH − follitropin alpha and follitropin beta), urinary FSH (uFSH), and highly purified uFSH (HP-uFSH). The rFSH and uFSH have been found to be equally effective;[140,141] however, the cost-minimization analysis showed that rFSH had a 9.4% reduction in the overall therapy cost per born baby in PCOS patients with CCR.[142]

Protocols: The step-up chronic low-dose protocol remains the best first-line approach for PCOS. In the step-up chronic low-dose protocol, the starting dose should be 37.5–75 IU, depending on patients' age and BMI, for 7–10 days. If there is no development of a follicle ≥12 mm in size, the gonadotropin dose is increased step by step for the subsequent 7 days by half. Ovulation is triggered when there is the development of a leading follicle ≥18 mm in size in the absence of any other follicles in excess of 14 mm in size.[143] In women where step-up protocols are not successful, step-down protocol, which works on reverse principles, can be attempted. A higher initial dose (100–150 IU) results in a deliberate multifollicular recruitment, and the secondary reduction in FSH leads to the development of only the most sensitive follicle.[144,145] Although the efficacy of both "step-up" and "step down" protocols are comparable, the step-up approach is much safer in terms of excessive ovarian stimulation and OHSS and potentially easier to monitor.[146]

It is mandatory to monitor the progress of follicle growth periodically, right before the initiation of each cycle and during stimulation with gonadotropins. Serial TV-USG

should be used to monitor follicle size (particularly those >10 mm) to predict the risk of multiple pregnancies. In most previous studies, to prevent OHSS and multiple pregnancies, cycle cancellation has been advised when more than three follicles of 16 mm or larger were observed.[147-149] However, in women with PCOS under the age of 38 without any other infertility factors, to minimize the risk of multiple pregnancies, it is judicious to stop human chorionic gonadotropin (hCG) administration as per the American Society of Reproductive Medicine (ASRM) criteria of presence of >2 follicles ≥16 mm or >1 follicle ≥16 mm and 2 additional follicles ≥14 mm. Similarly, serum estradiol levels are also measured to minimize the risk of OHSS or multiple pregnancies and adjust the gonadotropin dose in the step-up or step-down protocols or cancel the induction cycle (because of excessive/poor response). The ASRM practice bulletin, 2006 suggests caution if a rapid rise in serum estradiol levels or serum concentrations >2500 pg/mL is observed with gonadotropin stimulation.[150] However, much lower serum threshold concentrations of estradiol (<1000 pg/mL), close to clinical practice according to the number of growing follicles, are reported in other studies.[151,152] The intensive diagnostic monitoring and cost of treatment with injectable gonadotropins has to be discussed with the individual woman before initiation.

A prediction model consisting of presence of oligo/amenorrhea, duration of infertility, and free androgen index allowed a distinction to be made between women with a poor chance and women with a good chance of achieving an ongoing pregnancy.[153] In another model, the individual FSH response dose in anovulatory infertile women was predicted on the basis of BMI, ovarian response during previous CC therapy, and serum levels of free insulin-like growth factor 1 and FSH.[154] A live birth prediction chart has been developed for various OI methods using clinical measures.[155]

Current evidence

In randomized trials, pregnancies and live births were achieved more effectively and faster after OI with low-dose FSH than with CC.[156,157] However, this result required to be balanced by convenience and cost in favor of CC.[158] In a randomized trial, CC coadmin istered during low-dose HP-uFSH versus rFSH for CC-resistant PCOS yielded significantly higher ovulation rate and less consumption of FSH.[159] In the Indian scenario, a large prospective clinical trial conducted in PCOS patients treated with a combination of CC and uFSH compared to CC alone found high ovulation and pregnancy rate.[160] In a meta-analysis, metformin administration increased the live birth and pregnancy rate in PCOS patients who received gonadotropins for OI. The meta-analysis concluded that there was a lack of adequately designed, blinded, placebo-controlled, and satisfactorily powered RCTs to confirm the results.[161]

Existing recommendation

All current clinical practice guidelines recommend gonadotropins as second-line therapy in PCOS patients with CCR with strict monitoring for OHSS and multiple pregnancies.[16-18,72,102] Moreover, counseling of patients about the risks associated with higher-order multiple pregnancies after polyovulation with gonadotropins and cost of treatment is recommended by all current guidelines.[16-18,72,102] However, Australian alliance recommends gonadotropins as first-line pharmacological therapy in women with PCOS who are therapy naïve, anovulatory, and infertile, with no other infertility factors (Grade C). ESHRE 2008 and ASRM 2008[162] recommend starting dose of gonadotropin as 37.5–50 and 37.5–75 IU/day, respectively, with a duration not exceeding six ovulatory cycles, with the subsequent cycle beginning at the threshold of response previously determined.

Recommendations on Gonadotropins and GnRH analogs

1. Gonadotropins are recommended as a second-line treatment for not exceeding three ovulatory cycles in PCOS women with CCR or failure to conceive who are anovulatory and with no other subfertility factors (Grade A, EL 2).
2. When gonadotropins are indicated, it is recommended to counsel patients on the need for strict monitoring of cycle, the risk of OHSS and multiple pregnancy, the cost of treatment, and cycle cancellation criteria before treatment initiation (Grade B, EL 4).
3. When gonadotropins are indicated, the low-dose step-up protocol is recommended over step-down protocol to reduce the chances of OHSS in PCOS patients with subfertility (Grade A, EL 2).
4. The recommended starting dose of gonadotropin is 37.5–50.0 IU/day for 7–10 days, with small dose increments of 50% of the initial or previous dose if follicle ≥12 mm is not developed, and ovulation is triggered when there is the development of a leading follicle ≥18 mm in size (Grade B, EL 4).
   or
   The recommended starting dose of gonadotropins (as indicated in Table 2) should be given for 7–10 days, with small dose increments of 50% of the initial or previous dose if follicle ≥12 mm is not developed, and ovulation is triggered when there is the development of a leading follicle ≥18 mm in size (Grade B, EL 4).

Table 2: The representative recommended starting dose of gonadotropins

Gonadotropin	Dose (IU/day)
uFSH	75
HP-uFSH	37.5
hMG	75
rFSH-follitrophin alpha	37.5
Follitrophin beta	50

Aromatase inhibitors

Aromatase inhibitors (AIs), originally developed for the treatment of advanced breast cancer in postmenopausal women, have been used extensively as oral ovulation-inducing drugs in anovulatory women over the last decade.[163] Letrozole and anastrozole are the most commonly used AIs for OI. They act by increasing the pituitary secretion of FSH by inhibiting estrogen biosynthesis by a negative feedback mechanism. Henceforth, stimulating the ovary, accompanied by increased sensitivity to FSH, leads to follicular growth and development.[164,165]

AIs score over CC for the OI in anovulatory PCOS women in terms of avoiding adverse effects (peripheral antiestrogenic effects on the endometrium and cervical mucus) and lower risk of multiple pregnancy.[166,167] The effects on thinning of endometrial lining and estrogen receptors centrally are also not seen with the use of AIs.

Dosing: On day 3–7 of the menstrual cycle at doses of 2.5–7.5 mg/day (2.5 mg increments), letrozole is admin istered.[168] Gastrointestinal disturbances, asthenia, hot flushes, headache, and back pain are the few adverse effects observed.[164] The higher risk of congenital cardiac and bone malformations in newborns has been reported with use of letrozole.[169] Nevertheless, two subsequent publications suggest that letrozole use for OI may not be associated with increased risk of fetal anomaly.[170,171] Letrozole is not approved for OI. Yet, physicians often use this medication in an "off-label" way. Hence, until AIs have been approved for OI by regulatory authorities, they should be used with caution.[165]

Evidence

There is only one evidence on the effectiveness of AIs as first-line therapy for infertility management in women with PCOS. The recent Pregnancy in Polycystic Ovary Syndrome II (PPCOSII) RCT compared CC versus letrozole for anovulatory infertility in women with PCOS and reported a significant difference in ovulation (61.7% for letrozole vs. 48.3% for CC, $P < 0.0001$) and live birth rates (27.5% for letrozole vs. 19.2% for CC, $P = 0.007$).[172] Further, a 44% higher live birth rate was observed with letrozole in the cohort with high BMI and long-standing infertility. Therefore, letrozole with its oral route of administration, safety profile, and effectiveness in OI and ovarian stimulation is an attractive option and can be considered the first-line option for induction of ovulation in PCOS women.

In a meta-analysis of 26 RCTs, letrozole was found to improve live birth and pregnancy rates in subfertile women with anovulatory PCOS, compared to CC. There was no difference in effectiveness between letrozole and LOD, though there were few relevant studies. OHSS was a very rare event.[173]

All the other available studies address letrozole as second-line therapy in PCOS.

In a randomized trial, letrozole was found better than placebo for ovulation rate per patient, whereas for pregnancy rate or live birth rate per patient, the results were comparable.[174] Two RCTs compared letrozole to anastrozole. There was no difference between letrozole and anastrozole for ovulation rate per cycle, pregnancy rate per cycle, and miscarriage rate per pregnancy in PCOS women with CCR. The first study found that letrozole is better than anastrazole; however, the results of this low-quality study should be interpreted with caution.[175,176] One RCT found that long-term therapy (10 days) of letrozole was better than short-term therapy (5 days) for pregnancy rate per cycle in women with CC-resistant PCOS. There was no difference between long-term therapy of letrozole and short-term therapy for ovulation rate per patient and miscarriage rate per pregnancy in women with CCR PCOS. This is the only study identified addressing the duration and dose of letrozole, and the 10-day protocol using 2.5 mg/day appeared optimal.[177]

In a meta-analysis by Australian alliance, letrozole was better than CC for ovulation rate per patient. However, there was no difference between letrozole and CC for ovulation rate per cycle, pregnancy rate per patient, live birth rate per pregnancy, miscarriage rate per pregnancy, and multiple pregnancy rates per patient.[18] One medium-quality RCT (level II) with moderate risk of bias compared letrozole to CC plus metformin and found that there was no difference between letrozole and CC plus metformin for ovulation rate per cycle, pregnancy rate per cycle, miscarriage rate per pregnancy, and multiple pregnancy rate per pregnancy in women with CCR PCOS.[178] In a randomized trial, both metformin plus letrozole and bilateral ovarian drilling were similarly effective as second-line strategies for the treatment of women with PCOS who did not conceive with CC.[179] In

a randomized trial, there was no difference between two protocols of letrozole starting on days 3 and 5 of menstrual cycle on ovulation and pregnancy rate in CCR PCOS patients undergoing intrauterine insemination (IUI).[180] In a prospective, randomized study, letrozole was superior to tamoxifen in achieving a higher pregnancy and ovulation rate and had lesser side effects in CCR PCOS patients.[181]

Indian scenario

In the Indian context, RCTs demonstrated that letrozole significantly increased the ovulation rate compared to placebo and improved endometrium and pregnancy rate compared to CC in anovulatory PCOS women with subfertility.[174,182] In a prospective, randomized trial by Kar,[183] letrozole had excellent pregnancy rates compared to CC and recommended letrozole as the first-line drug for OI in infertile PCOS at par with CC. In a prospective, randomized trial by Ganesh *et al.*,[184] letrozole was found to be most effective compared to gonadotropins or gonadotropins plus CC, especially when baseline estradiol level >60 pg/mL. In a randomized trial by Roy *et al.*,[185] letrozole and CC had comparable ovulation rate. In a study by Baruah *et al.*,[186] letrozole showed a significantly better endometrial response compared to CC.

Existing recommendation

1. ESHRE does not address AIs for recommendations because of lack of evidence at that point in time.[16–18,72,102]
2. Australian guideline states that letrozole should not be a first-line (Grade B) pharmacological therapy in women with PCOS and recommend using either letrozole or anastrozole in women with CCR, and who are anovulatory and infertile with no other infertility factors. The recommended dose of letrozole 2.5 mg/day is for 10 days (Grade D).
3. In women with PCOS, ESE recommends CC (or comparable estrogen modulators such as letrozole) as the first-line treatment.
4. SOGC has not made any recommendation on AIs but states that it should be used with caution considering the congenital malformations until approved for OI by Health Canada.

Recommendations on aromatase inhibitors

1. In anovulatory and subfertile PCOS patients with CCR with no other subfertility factors, administration of AIs (letrozole 2.5 mg/day for 10 days) is suggested, after gonadotropin failure. However, since AIs are not indicated for OI, the use will be considered off-label.
2. In patients with breast cancer and PCOS requiring oocyte cryopreservation, AIs are recommended.
3. PCOS women administered with AIs should be counseled about the risk of congenital malformations.

LAPAROSCOPIC SURGERY

Surgical therapy can be a more intensive second-line therapy for OI in women with PCOS. Risks and benefits should be well considered by the patient and clinician together. LOD aims to induce ovulation.

The main indications for the use of LOD in women with anovulatory PCOS, as an alternative to gonadotropins, include patients with the following conditions:

1. CCR.
2. Persistently hypersecretion of LH, either during natural cycles or in response to CC.
3. The need for laparoscopic assessment of their pelvis.
4. Poor access to healthcare facilities (living far or other practical reason) for intensive monitoring required during gonadotropin therapy.

The RCOG, ACOG, SOGC, and the recent PCOS consensus working group all recommend its use in highly selected cases as the above.[16,17,72,187]

LOD uses either cautery or laser to create superficial perforations, but there is no difference in outcomes between the two modalities.[188-190] Ovarian surgery may also be performed transvaginally by hydrolaparoscopy.[191] The degree of thermal stromal damage and number of punctures should be determined by the size of the ovary.[192] Originally, 3–8 diathermy punctures (each of 3 mm diameter and 2–4 mm depth) per ovary were applied for 2–4 s with 200–300 W power setting. However, increasing the dose up to 600 J/ovary has also been reported.[193] Recently, adjusting thermal dose based on ovarian volume (60 J/cc) had better reproductive outcomes than fixed dose of 600 J/ovary, with similar postoperative adhesion rates.[194] Unilateral ovarian drilling was found to be equally efficacious as bilateral ovarian drilling in terms of ovulation and pregnancy rates in a randomized trial.[195] A line of evidence shows obesity (BMI > 25 kg/m^2), high basal AMH ≥ 7.7 ng/mL, low basal LH levels <10 IU/L, long duration of infertility >3 years, and marked biochemical hyperandrogenism (testosterone levels ≥4.5 nmol/L and free androgen index >15) as the predictors of poor response of LOD.[196,197]

The advantages of LOD in patients with CCR include the endoscopic approach, which causes fewer adhesions, is more

cost effective, and restores regular mono-ovulations, although for a limited time in the majority of the cases. On the contrary, treatment with gonadotropins often results in the development of multiple mature follicles, is expensive, and requires regular monitoring with a potential risk of multiple pregnancies and OHSS.

Current evidence

A high-quality RCT (level II) with a low risk of bias found that LOD was not superior to CC as a first-line method of OI in women with PCOS.[198] There is an insufficient evidence to make a recommendation about LOD compared to metformin because of the conflicting results of randomized trials.[199-201] An RCT by Hamed *et al.*[199] demonstrated that LOD was better than metformin for ovulation and pregnancy rate, while other studies have shown metformin better than LOD for live birth rate (metformin: 82.1%, LOS: 64.5%, $P < 0.05$), pregnancy rate per cycle (metformin: 18.6%, LOS: 13.4%, $P < 0.05$), and miscarriage rate (metformin: 15.4%, LOS: 29.0%, $P < 0.05$).[200,201] Similarly, an RCT by Palomba *et al.*[202] has shown CC plus metformin better than LOD for ovulation rate per cycle but there was no difference for the live birth rate per cycle, pregnancy rate per cycle, and miscarriage rate per pregnancy in CCR patients.

A systematic review of RCTs compared LOD to gonadotropins and found that there was no difference between the interventions for the live birth rate per patient and pregnancy rate per patient, ovulation rate per patient and miscarriage rate per pregnancy, but LOD was better than gonadotropins for multiple pregnancy rates.[190] In another meta-analysis, no evidence of a significant difference in rates of clinical pregnancy and miscarriage in PCOS women with CCR undergoing LOD compared to the gonadotropin arm was observed. The decrease in multiple pregnancies rate in women undergoing LOD makes this option attractive. The higher rate of multiple pregnancy resulted in an increase in live birth rate in the gonadotropin group in these women.[203] Despite the evidence that LOD may be equivalent to gonadotropins in achieving ovulation, the effects of LOD on postoperative adhesion formation remain a concern.[204] In ~50% of LOD-treated women, adjuvant therapy will be required; the addition of CC or FSH can be considered after 12 weeks or 6 months, respectively if no ovulation is detected.[205]

In a prospective study by Kriplani *et al.*, LOD in PCOS patients with CCR resulted in spontaneous ovulation rate of 81.8%, cumulative ovulation rate of 93.9%, and pregnancy rate of 54.5%. The predictors of better response were elevated LH levels (>10 IU/L), the absence of preexisting tubal disease, and short duration of infertility (<3 years).[206] Another prospective, rando mized study found no difference between unilateral versus bilateral LOD for ovulation rate and pregnancy rate when the number of a drilling site in each ovary was limited to five.[207]

From the above evidence, it can be concluded that there is insufficient evidence to support or negate the use of LOD over metformin or CC or CC plus metformin for multiple pregnancies and there is insufficient evidence to support or disprove the use of LOD over any intervention for adverse effects and QoL.

Existing guidelines

All the existing guidelines recommend LOD as an alternative to gonadotropin therapy for CC-resistant anovulatory PCOS.[16-18,72,102] Moreover, Australian Alliance 2010, RCOG 2014, and SOGC 2010 guidelines recommend LOD as the first-line therapy for OI, if laparoscopy is indicated for another reason in infertile women with PCOS.

Recommendations on laparoscopic surgery

1. In anovulatory PCOS women who are CCR and have hypersecretion of LH levels with no other subfertility factors, laparoscopic ovarian surgery is recommended as second-line therapy over gonadotropin therapy (Grade A, EL 1).
2. The number of punctures should depend on the size of ovary but it should be limited to a maximum of 4–6 (Grade B, EL 4).
3. In anovulatory PCOS women with CCR and with no other subfertility factors, who cannot access hospital facility for intensive monitoring, required with gonadotropin therapy or requiring laparoscopic assessment of their pelvis, it is suggested to attempt LOD (Grade C, EL 4).
4. LOS should not be offered for nonfertility indications, severe male factors or women with obstructive tubal disease.

ASSISTED REPRODUCTIVE TECHNOLOGY

The assisted reproductive techniques comprise of IUI and IVF.

Intrauterine insemination

Indications[208,209]

The expert panel of ESHRE recommends combining OI with IUI in women with PCOS if there is an associated male subfertility.[210] IUI is indicated in women with

PCOS who failed to conceive despite successful induction of ovulation. The efficacy of such treatment ranges from 11 to 20% clinical pregnancy rate per cycle with a multiple pregnancy rate ranging from 11 to 36% based on a limited number of studies on women with PCOS.[16] With IUI, careful monitoring is required to reduce the risk of OHSS and multiple pregnancies. TV-USG-guided aspiration of the surplus follicles may be an approach to reduce the risk.[211,212] Semen preparation is necessary before IUI, but there is insufficient evidence to recommend any specific preparation technique. From the available evidence, no significant benefit in pregnancy rate was observed with double insemination over single IUI.[213-215]

Current evidence

A randomized trial comparing three consecutive OI cycles of CC with either IUI or timed intercourse as first-line treatment for anovulatory infertility in 188 therapy-naive women with PCOS (525 cycles) has shown comparable outcomes between the two treatment groups with no difference in clinical pregnancy rate per cycle (8.5 vs. 7.9%; $P = 0.26$) or per woman (23.6 vs. 22.1%; $P = 0.33$), miscarriage rate per pregnancy (18.1 vs. 19.0%; $P = 0.31$), and live-birth rate per woman (19.3 vs. 17.9%; $P = 0.33$), respectively. Therefore, the addition of IUI to the first three cycles of CC does not improve reproductive outcomes for the PCOS woman where anovulation is the sole cause for infertility.[216]

Multiple pieces of evidence of OI with different agents in the IUI cycle are documented. Letrozole and CC had similar OI and pregnancy rate after a single cycle of IUI in an RCT.[217] In contrast, in another RCT, letrozole had a significantly greater effect on endometrial thickness than CC, and the incidence of pregnancy after IUI was significantly higher, with a lower incidence of multiple pregnancies.[218] Similar results were observed in an Indian randomized trial; the ovulation and pregnancy rates were relatively beneficial with letrozole (79.3, 23.39%) than CC/rFSH alone (56.95%, 14.35%) and rFSH (89.89%, 17.92%) alone groups. The miscarriage rates were 13.80%, 16.67%, and 14.52%, respectively.[184] In another RCT, administration of GnRH antagonist in women with PCOS resulted in less premature luteinization, more monofollicular development, and less cycle cancellation in IUI cycles. This observation is supported by a meta-analysis of RCTs for GnRH antagonist use in IUI cycles.[219,220]

Existing guidelines

ESHRE recommends IUI in women with PCOS and an associated male factor, and in women who failed to conceive despite successful ovulation.

Recommendations on intra-uterine insemination

1. In anovulatory subfertile PCOS women with associated male factor subfertility, IUI is recommended along with OI.
2. In anovulatory subfertile PCOS women with unsuccessful conception despite OI, IUI is recommended.

In vitro fertilization

IVF is indicated with or without intracytoplasmic sperm injection (ICSI) in patients who fail to conceive with first-line or second-line treatments. IVF is appropriate in women with PCOS who do have associated pathologies such as in the case of tubal damage, severe endometriosis, and preimplantation genetic diagnosis and male factor infertility.[221]

During IVF, ovulation-inducing agents are administered to promote multifollicular development in the anovulatory PCOS women with continuous monitoring. When at least three follicles reach ≥17 mm size, hCG is administered to trigger oocyte retrieval. The oocytes are collected usually after 35 h after trigger and processed *in vitro* to generate embryos for transfer into the uterus. From the existing evidence, milder stimulation protocols are recommended, at least for the first cycle of IVF to avoid over stimulation in PCOS women. Although pregnancy rates up to 40–50% per cycle are achieved with IVF, as with fertility in general, the success of the procedure is significantly influenced by the women's age.

Current evidence

Irrespective of the PCOS status, patients undergoing conventional IVF cycles achieve similar pregnancy and live birth rates,[222] meaning PCOS does not affect the stability of formed embryo. This is supported by, a prospective, observational study, in which similarly transferred embryo numbers, clinical pregnancy rates, and implantation rates were seen between PCOS and non-PCOS patients; incidence of OHSS was much higher in the PCOS and ovulatory polycystic ovary patients.[223] The IVF is associated with the risk of OHSS (10% in patients with PCOS vs. 0.5–4% in non-PCOS) and multiple pregnancies when multiple embryos are transferred.[224]

Broadly, the commonly used IVF protocols are GnRH agonist or GnRH antagonist protocols. Several agonist and antagonists agents are being extensively studied in clinical practice.[225,226] In terms of clinical embryological and pregnancy rate, the GnRH antagonist protocol is similar to GnRH agonist long protocol.[227] The evidence

is emerging in favor of using antagonist protocol over agonist protocol in PCOS women.[227-231] Similarly, studies from India also show GnRH antagonist protocol equally effective but safer than long agonist protocol in PCOS patients.[232,233] Advantages of antagonist protocols are that it is more patient friendly owing to shorter duration of administration, and has a lower incidence of OHSS and cycle cancellations.[227-231] Further, in PCOS woman (≤30 years) undergoing IVF, the sequential step-up/step-down stimulation protocol was more efficient to the low-dose step-up and step-down regimens in terms of OI, pregnancy rate, and miscarriage rate.[234] Administration of OCP to norm alize the LH/FSH ratio before controlled OI for IVF did not show any beneficial effects in terms of follicular growth, number of oocytes, and quality of oocyte and embryo;[79,235,236] however, improved pregnancy rate was found in only one retrospective study.[237] The total number of oocytes retrieved (14.17 ± 4.89 vs. 13.03 ± 5.56, $P = 0.17$), the quality, number of embryos (7.63 ± 3.28 vs. 7.42 ± 3.35, $P = 0.68$), incidence of OHSS, and the rates of clinical pregnancy (45% in uFSH and 41.2% in rFSH, $P = 0.67$) were similar in PCOS patients treated with rFSH verses uFSH.[238] However, rFSH prod uced higher pregnancy rate per cycle than uFSH in patients undergoing IVF in a meta-analysis of 18 trials.[239]

Existing guidelines

ESHRE 2008, SOGC 2010, and Australian alliance 2011, recommend IVF as a third-line treatment, and are reserved for women who fail to conceive despite successful OI and have associated male infertility.[16,18,72] These guidelines do not specify optimal stimulation protocol with the use of GnRH agonist versus GnRH antagonist. However, using GnRH antagonist protocol for known or suspected high responders is recommended by the British Fertility Society Policy and Practice Committee including women with PCOS, as it reduces the risk of OHSS.[240]

Indian GCPR

1. IVF is a third-line treatment option in women with PCOS who fail to conceive or who have other indications for IVF (Grade A, EL 2).
2. In anovulatory subfertile PCOS women with no other causes of subfertility, initiating IVF cycles along with OI is recommended as a third-line treatment option (Grade C, EL 4).
3. In anovulatory subfertile PCOS women indicated for IVF, the GnRH antagonist protocol can be suggested over the GnRH agonist long protocol because of reduced incidence of severe OHSS at similar clinical pregnancy rates (Grade A, EL 2).
4. The recommended starting dose of gonadotropin is 75–300 IU/day for 7–10 days depending on age and follicle size, and ovulation is triggered when there is the development of at least three leading follicles ≥17 mm in size (Grade B, EL 4).

LUTEAL PHASE SUPPORT

The period between OI and establishment of pregnancy is called luteal phase. During this phase, progesterone produced from corpus luteum helps establish a pregnancy. The granulosa cells of women with PCOS may have an inherent inability to secrete normal levels of progesterone after luteinization if ovulation is achieved. Luteal phase insufficiency can be attributed to a defect in follicle growth and inadequate production of progesterone. Hyperinsulinemia or IR may also impact progesterone levels during the luteal phase in women with PCOS.[241] In fact, the controlled ovarian hyperstimulation negatively affects LH secretion that leads to premature luteolysis, reduced LH concentration, low progesterone level, and shortened luteal phase, leading to improper implantation and decreased pregnancy rates. Therefore, luteal phase in women with PCOS is supported with progesterone,[242] which can transform the uterine glands for secretions, increase the vascularity of endometrial lining, and stabilize the endometrium in preparation for embryo implantation.

Current evidence

Luteal phase support with vaginal progesterone has demonstrated higher pregnancy rate and live birth rate by 6.7 and 6.1%, respectively, than placebo in CC-resistant PCOS women who underwent IUI with OI using gonadotropins.[242] In a study by Foroozanfard *et al.*,[243] intravaginal progesterone supplementation in luteal phase starting from the day of hCG trigger resulted in 10% higher pregnancy rate in women with PCOS using letrozole or CC in combination with hMG for OI than in nonprogesterone cycles. In a meta-analysis, the evidence suggested that in assisted reproductive technology (ART) cycles, higher rates of live birth or ongoing pregnancy were observed with progesterone supplementation during the luteal phase than with placebo. The addition of GnRH agonist to progesterone appears to improve outcomes.[244] In another meta-analysis, probability of live birth rate and clinical pregnancy rate was significantly higher in patients who received GnRH analogue for luteal support in IVF/ICSI cycles compared with those who did not. Cotreatment with GnRH agonists further improves outcomes, by a live birth rate (risk difference: 16%, 95% CI 10–22%).[245] Transdermal E2 supplementation as an addition to the

luteal phase progesterone for IVF cycles does not improve implantation and pregnancy rates in PCOS patients.[246] hCG should be avoided for luteal support as hCG with or without progesterone is associated with higher rates of OHSS than progesterone alone. These studies support that luteal supplementation with progesterone should be strongly considered in women with PCOS. The optimal form, dosage, and timing of progesterone have to be ascertained for each individual. Depending on the successful implantation, the luteal support is continued till the first trimester.[247]

In terms of route of administration, progesterone vaginal insert was a more convenient method for providing luteal phase support for IVF cycles compared to intramuscular progesterone in oil, with similar pregnancy rates in both groups.[248] Similarly, the evidence suggests that the improvement in live birth rate or ongoing pregnancy rate in ART cycles is independent of the route of administration of progesterone.[244] Further, a recent meta-analysis compared luteal support using oral dydrogesterone and vaginal micronized progesterone in women undergoing ART for pregnancy. No significant difference was observed between oral dydrogesterone and vaginal progesterone on ongoing pregnancy (RR 1.04, 95% CI 0.92–1.18, $I^2 = 0\%$, 7 RCTs, 3134 women), on clinical pregnancy (RR 1.07, 95% CI 0.93–1.23, $I^2 = 34\%$, 8 RCTs, 3809 women), and on miscarriage (RR 0.77, 95% CI 0.53–1.10, $I^2 = 0\%$, 7 RCTs, 906 clinical pregnancies),[249] Similar reports on equivalent efficacy but significantly higher patient satisfaction rates with tolerability ($P < 0.05$) were documented from RCTs in India.[250] As per the evidence, there appears to be a window for progesterone start time for luteal support between the evening of oocyte retrieval and day 3 after oocyte retrieval, but potential benefit in pregnancy rate was observed when vaginal progesterone was started 2 days after oocyte retrieval.

Existing guidelines

The National Institute for Health and Care Excellence 2013 guidelines recommend luteal phase support with progesterone in IVF cycles.[88]

Recommendations for luteal phase support

1. Administration of luteal phase progesterone is recommended in subfertile PCOS women undergoing OI or assisted reproduction (Grade A, EL 1).

FUTURE PROSPECTS

Melatonin, N-acetyl cysteine (NAC), and myo-inositol have emerged as novel pharmacotherapeutics to improve IVF outcomes for the treatment of infertility. At present, there are only a few studies addressing their role in infertility associated with PCOS.

N-acetyl cysteine

The current evidence on the role of NAC as stand-alone therapy compared to metformin or metformin with CC is controversial. In a randomized trial, metformin alone was an effective drug in inducing ovulation in CC-resistant PCOS, whereas NAC alone was not.[251] In another trial, metformin-CC combination therapy was superior in OI, achieving pregnancy among CC-resistant PCOS patients compared to NAC-CC.[252] Conversely, NAC was effective in inducing or augmenting ovulation in PCOS patients in a prospective crossover trial.[253]

Melatonin

Melatonin, or N-acetyl-5-methoxytryptamine produced by mammalian pineal gland, possesses antioxidative, anti-inflammatory, antiapoptotic, endocrinologic, and beha vioral effects. The constructive outcome of melatonin on the reproductive system is well documented.[254-257]

The mean number of the retrieved oocytes, the mean metaphase-II oocyte counts, and the G1 embryo ratio were significantly higher in the melatonin-treated patients than the controls in a randomized study.[258] In another randomized study, the percentage of mature oocytes was significantly high in melatonin-treated patients compared to control. However, clinical pregnancy rate was similar in both groups.[259] When melatonin was added to myo-inositol and folic acid, it resulted in an increased number of mature oocyte retrieval in randomized trials.[260] In a study by Kim *et al.*, addition of melatonin to *in vitro* maturation (IVM) medium improved cytoplasmic matura tion of human immature oocytes and subsequent clinical outcomes in PCOS.[261]

In a meta-analysis that included 5 RCT, the results were imprecise for distinguishing between no effect and benefit considering clinical pregnancy, number of oocytes retrieved, % of miscarriage, and risk of OHSS. Further studies investigating the role of melatonin supplementation are warranted before recommending its use in clinical practice.[262]

Myo-inositol

Myo-inositol (d-chiro-inositol) is a vitamin factor belonging to vitamin B complex group. In women with PCOS, its benefits include the following: increase in insulin sensitivity, affirmative effects on ovulation, and androgen production. The administration of d-chiro-inositol was associated with a

decreased serum testosterone and increased sex hormone-binding globulin (SHBG) concentration in PCOS.[263] Improvement in the ovulatory function has been shown with myo-inositol. It improves oocyte quality (reduction of the total amount of the germinal vesicles and the degenerated oocytes) and a number of mature oocytes collected in PCOS patients undergoing IVF or ICSI.[264,265] In a randomized trial, myo-inositol was found to improve the yield of mature oocytes in PCOS.[266]

In vitro maturation

In women with PCOS, use of gonadotropins at physiological/supraphysiological doses for OI often causes an exaggerated ovarian response. This is characterized by the generation of follicles of uneven quality, increased risk of OHSS, and retrieval of immature oocytes for IVF. Therefore, early retrieval of oocytes at germinal vesicle stage and process for IVM can be an effective alternative for women with PCOS-related subfertility. Further, from the recent evidence on cancer patients requiring rapid fertility preservation/at risk of estrogen-sensitive cancer recurrence, IVM has been proposed as the method of choice.[267]

On the basis of these, the indications for IVM can be derived as follows:

1. Women with PCOS or PCO-like ovaries,
2. Women at risk of OHSS,
3. Women with estrogen-sensitive cancers, and
4. Women requiring rapid fertility preservation before beginning gonadotropin therapy.

IVM outcomes in PCOS

Evidence from the observational and retrospective studies in the last two decades using IVM in patients with PCOS is promising. From the observational studies in PCOS women, high oocyte maturation rates (up to 80.3%), fertilization rates (10–76.5%), clinical pregnancy rates (21.5–55% per cycle), implantation rates (~18%), and live birth rates (15.9%/retrieval to 33%/cycle) were reported.[268-272] A latest retrospective study that compared the outcomes of IVM and IVF-GnRH antagonist protocols in PCOS women using ARTs for conception reported similar amount of mature oocytes (7.11 ± 5.7 vs. 8.16 ± 5.07, $P = 0.38$), pregnancy rates (40 vs. 25%; $P = 0.08$), live birth rates per pregnancy (71 vs. 53%; $P = 0.265$), and abortion rates (10 vs. 27%; $P = 0.17$).[273] Hence, in infertile women with PCOS who desire to avoid the adverse effects of gonadotropin treatment, IVM protocol can be an alternative.

The IVM clinical protocols and culture technology need further improvement. Therefore, since the amount of evidence from RCTs is low, it may be preliminary to provide any practice recommendations regarding IVM before IVF or ICSI for women with PCOS.

Split cycles for embryo transfer

Controlled ovarian stimulation with exogenous gonad otropins leads to embryo–endometrium asynchrony, which impairs endometrial receptivity in cycles of IVF leading to reduced pregnancy rate in the fresh ET cycles. In this context, the frozen-thawed embryo transfer (FET) is an option that enables the excess embryos generated by IVF and ICSI to be stored and utilized at a later date. Further, in PCOS, there is a tendency to produce a large number of oocytes and embryos; this could result in higher incidence of OHSS. Further, implantation rate might be affected because of high level of E2.[274] Therefore, cryopreservation of all gametes for later transfer is ideal for PCOS patients.[275] This minimizes the wastage of embryos after IVF and improves conception chances/rate after a cycle of ovarian stimulation and oocyte retrieval.

The split-cycle IVF comprises endometrial preparation followed by transfer of human frozen-thawed embryos. The aim of FET protocols was to sufficiently prepare the endometrium to receive the thawed, transferred embryo. There are three groups of protocols as the following: follicular stimulation, hormone replacement (artificial cycle), and natural cycle protocols. Follicular stimulation protocols are least used in clinical practice owing to limited flexibility, frequent monitoring, and high cost. However, the superiority, regarding ongoing pregnancy rate and patients preference, of one approach over the other remains unclear. In a systemic review and meta-analysis by Groenewoud *et al.*,[276] no protocol was found more effective than another and they appeared to be equally successful in achieving the ongoing pregnancy rate. Pregnancy rates after cryopreservation may be significantly improved by selecting the right embryos for transfer. The cleavage capacity was found to be a good indicator of embryo viability in terms of pregnancy outcome.[277] No significant difference was noticed between FETs made with the transfer of embryos with overnight culture and those without culture. Significantly higher PR was achieved with transfer of embryos cleaved during overnight culture than transfers without any cleavage.[277] The results of the latest trial, FreFro-PCOS, comparing live birth after fresh embryo transfer versus elective embryo cryopreservation/FET in women with PCOS undergoing IVF, are awaited.[278] In a prospective study in India, the mean endometrial thickness, clinical pregnancy rate, live birth rate, and implantation rate were similar in artificial cycle FET with estradiol and progesterone versus hMG with or

without estradiol in PCOS.[279] In a retrospective study by Hu *et al.*,[280] letrozole-treated patients had a significantly higher maximal endometrial thickness and markedly higher rates of clinical pregnancy per transfer, ongoing pregnancy per transfer, and implantation, relative to artificial (estrogen and progesterone supplementation) and hMG stimulation groups.

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Conflicts of interest

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