

Management of Infertility in Patients from India with Polycystic Ovary Syndrome

A Consensus Evidence-based
Good Clinical Practice Recommendations

A Short Handbook



**INDIA'S FIRST
INFERTILITY
GUIDELINE**



Management of Infertility in Patients from India with Polycystic Ovary Syndrome : Consensus Evidence-based Good Clinical Practice Recommendations



An
Indian
Fertility
Society
Initiative

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FOREWORD

The Indian Fertility Society is committed to encouraging ethical evidence based practices amongst its members. All the activities of the society are centered on this basic ideology. In 2014 we published our first GCPR for PCOS in the country. The interest generated and the popularity of this guideline has prompted us to bring out a very much needed and extremely important GCPR.

It is with great pride that the Indian Fertility Society now brings to you the second part of the Good Clinical Practice Guidelines for PCOS in India. This particular guidance deals with the Management of infertility in PCOS in India.

PCOS is an enigmatic disorder having many phenotypes and resultant dysfunctions. Infertility forms a major symptom of the disorder. The treatment is varied because of the varied presentations. Hence, all kinds of management regimens are prevalent in the country. It is therefore important to bring uniformity in practice so that both the health care provider and the end user are benefitted. This guideline is an attempt to regulate management of the infertile couple in India. The evidence and recommendations are as per the requirements of the Indian patients.

I thank the members of the IFS writing group for taking pains in bringing out this document. My sincere thanks to Dr. Sohani Verma President IFS, for her constant encouragement and help.

I would like to put on record my grateful thanks to Mr Deepak Chopra and his team from Bayer Zydus Pharma Ltd. for their educational grant and unflinching support in bringing out this document and to Leena Patel from Jeewan Scientific Technologies for the technical support.

I once again thank IFS for its continuous support and belief in Good clinical practice.



With best wishes,

Dr Sonia Malik

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ABBREVIATION

AE	Androgen Excess
Als	Aromatase Inhibitors
CC	Clomiphene Citrate
CCR	Clomiphene Citrate Resistance
COCs	Combined Oral Contraceptive Pills
FSH	Follicle Stimulating Hormone
GnRH	Gonadotropin-releasing Hormone
IR	Insulin Resistance
IUI	Intrauterine Insemination
IVF	In-vitro Fertilization
LH	Luteinizing Hormone
LOD	Laparoscopic Operative Drilling
OCPSs	Oral Contraceptive Pills
OHSS	Ovarian Hyperstimulation syndrome
OI	Ovulation Induction
PCOS	Polycystic Ovarian Syndrome
RCT	Randomized Controlled Trial

Disclaimer

The contents of this document serve as a consensus based guideline regarding appropriate patient care practices based on the available medical literature and clinical expertise from India at the time of development. They should not be considered to be accepted protocol, policy or code of practice, nor are intended to replace good clinical judgment or dictate the care of individual patients.

Polycystic Ovarian Syndrome (PCOS)

Polycystic ovarian syndrome (PCOS) is a principal endocrine system disorder affecting women of reproductive age causing enlarged ovaries with small cysts on the outer edges. The cardinal features of PCOS are androgen excess (AE), chronic anovulation, and the presence of polycystic ovarian morphology¹. Further, insulin resistance (IR), increased gonadotropin-releasing hormone (GnRH) drive, and a proclivity for weight gain are observed in women with PCOS. Most women with PCOS are characterized by an elevated luteinizing hormone (LH)/ follicle stimulating hormone (FSH) ratio^{2,3}.

About 85%–90% of women with oligomenorrhea and 30%–40% of women with amenorrhea present with PCOS⁴. Approximately 13-19 million couples are likely to be infertile in India at any given time, and approximately 50% patients attending fertility clinics in India are diagnosed with PCOS⁵. In spite of remarkable growth and progress in the region of infertility management including those with anovulatory PCOS in India, several patients do not receive structured medical care based on the best available evidence due to lack of uniform practices in a clinical setting. This guideline directs 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.

Objective of the Meeting

1. To invite expert opinions from obstetrics and gynaecologists for the management and treatment of infertility in PCOS.
2. To discuss the current guidelines by various International Medical Organizations and strategize a wholesome approach.
3. Develop strategies to align the mind-set of Indian clinicians towards a common management of infertility in PCOS.

It was proposed to conduct a series of meetings with experts pan India. Systematic review of literature from the best possible evidence in the Indian scenario was conducted by a group of doctors and relevant recommendations were framed, and discussed by an expert panel (obstetrics, gynaecologists) in a series of meetings. In the areas where there was little or no evidence, the panel relied on experience, clinical judgment and consensus. The current consensus grading for recommendations are based on clinical importance (A: strongly recommended, B: suggested, C: unresolved) coupled by four intuitive levels of evidence (1='at least one randomized controlled trial (RCT) or meta analysis of RCTs', 2 = 'at least one non-randomized or non-controlled, prospective epidemiological study', 3 = 'cross-sectional or observational or surveillance or pilot study' and 4='existing guideline or consensus expert opinion on extensive patient experience or review').

1. 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-axis⁶. 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.

- The recommended diagnostic workup in subfertile women with PCOS includes the following:
 - 1) Clinical determination of 2 of the 3 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).

2. Patient Counseling: Pre And During The Treatment

- It is essential for the healthcare professionals to provide counseling on the physiological and emotional well-being of the subject with PCOS.
- 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)
- 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)
- It is recommended that healthcare professionals emphasize the role of the husband in emotional wellbeing of subfertile PCOS women during the course of treatment. (Grade B, EL 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)

3. Lifestyle modifications for weight reduction

Lifestyle modification envisioned to lessen body weight and overcome IR is the first line treatment in women with PCOS. Weight loss by lifestyle modification is the principal treatment for PCOS women before infertility management. After weight loss, patients should be encouraged to conserve this in the long run and to have normal weight gain during pregnancy⁷. However, treatment of obesity is multifaceted encompassing behavioral counseling, lifestyle modification (hypocaloric diet and exercise), pharmacological treatment, and bariatric surgery.

Recommendations

- 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)
- 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)
- The age-related decline in fertility should be given appropriate consideration for considering the duration of lifestyle management interventions. (Grade B, EL 4)
- In PCOS patients with subfertility who are morbidly obese (BMI >35 kg/m²), pharmacological methods of OI should be avoided before weight reduction. (Grade B, EL 4)
- Yoga is recommended as a part of lifestyle management work up as an aid for the treatment of subfertile PCOS women. (Grade B, EL 3)
- 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 serves as an effective outcome not only in weight loss, but also in the improvement of other PCOS conditions such as anovulation, metabolic syndrome and hyperandrogenism in PCOS women with morbid obesity (BMI ≥ 35 kg/m²)⁸. However, till date there is no documented evidence from India on the use of bariatric surgery as a means of weight reduction in PCOS women with infertility.

Recommendations

- Bariatric surgery is recommended as second-line treatment in morbidly obese (BMI >30 kg/m²) subfertile PCOS patients who are unsuccessful in achieving weight reduction by lifestyle modifications. (Grade B, EL 4)
- In PCOS patients with BMI >50 kg/m², bariatric surgery is suggested as first-line therapy for weight reduction. (Grade B, EL 4)
- 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).

4. Pharmacological intervention

4.1 Pre-treatment with Combined Oral Contraceptive (COC) pills

Combined oral contraceptive pills (COCs) reduce hyperandrogenism by promoting direct negative feedback on LH secretion thereby normalize the LH/FSH ratio leading to gradually increase for OI (OI)⁹.

Recommendations

- Low dose combined OCPs pretreatment (with or without lifestyle modifications) for at least 2 months is recommended in subfertile PCOS patients with high luteinizing hormone level (3 times the basal levels) to normalize it. (Grade B, EL 4)

4.2 Clomiphene citrate

Clomiphene citrate is a selective oestrogen receptor modulator with both oestrogenic and anti-oestrogenic properties. It releases hypothalamus from negative inhibition resulting in subsequent increase in FSH and LH production. Consecutively stimulates follicular growth leading to a midcycle LH surge and then ovulation^{10,11}.

Recommendations

- In anovulatory PCOS women with subfertility, CC is recommended as a first-line pharmacological agent at a starting dose of 50mg/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 6 cycles. (Grade A, EL 1)
- 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)

4.3 Insulin sensitizing agents

Insulin resistance affects approximately 65 to 80% of women with PCOS. The association of IR contributing to anovulation in PCOS and in an attempt to restore ovulation and improve the chances of pregnancy has led to the introduction of insulin-sensitising drugs¹².

Recommendations

- Metformin is recommended in the following circumstances:
 - In PCOS patients with impaired glucose intolerance (disturbed oral glucose tolerance test)
 - In obese PCOS, women co-administered with clomiphene
 - In CC-resistant PCOS women
 - In PCOS women who are at high risk of hyperstimulation
- 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. If side effects worsen with increased dose, the current dose is maintained for 2–4 weeks until tolerance is developed

4.4 Gonadotrophins and GnRH analogs

Gonadotrophin therapy is second-line therapy in anovulatory PCOS women with either CC resistance or failure to conceive¹³.

Recommendations

- Gonadotrophins 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)
- When gonadotrophins 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, cycle cancellation criteria before treatment initiation. (Grade B, EL 4)
- When gonadotrophins 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)

- 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 development of a leading follicle ≥ 18 mm in size. (Grade B, EL 4)

OR

- The recommended starting dose of gonadotrophins (as indicated in table below) 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 development of a leading follicle ≥ 18 mm in size. (Grade B, EL 4)

Table : The representative recommended starting dose of gonadotrophins

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

4.5 Aromatase inhibitors

Aromatase inhibitors (AIs) like letrozole and anastrozole are used extensively as oral ovulation-inducing drugs in anovulatory women over the last decade. They act by increasing the pituitary secretion of FSH by inhibiting oestrogen biosynthesis by a negative feedback mechanism⁹. Hence stimulates ovary, accompanied by increased sensitivity to FSH thus leading to follicular growth and development.

Recommendations

- 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 gonadotrophin failure. However, since AIs are not indicated for OI, the use will be considered off-label.
- In patients with breast cancer and PCOS requiring oocyte cryopreservation, aromatase inhibitors are recommended.
- PCOS women administered with AIs should be counseled about the risk of congenital malformations.

4.6 Laparoscopic surgery

Surgical therapy can be a more intensive second-line therapy for OI in women with PCOS. Laparoscopic operative drilling (LOD) is indicated in anovulatory PCOS women with clomiphene citrate resistance, persistent hypersecretion of LH, needing laparoscopic assessment of their pelvis and poor access to healthcare facilities (living far or other practical reason) for intensive monitoring required during gonadotrophin therapy¹⁴.

Recommendations

- 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 gonadotrophin therapy. (Grade A, EL 1)
- 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)
- 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)
- LOS should not be offered for non-fertility indications, severe male factors or women with obstructive tubal disease.

5. Assisted reproductive technology

The assisted reproductive techniques comprise of intrauterine insemination (IUI) and in-vitro fertilization (IVF).

5.1 Intrauterine insemination

- The ESHRE recommends combining OI with IUI in women with PCOS if there is an associated male subfertility. IUI is indicated in women with PCOS who failed to conceive despite successful induction of ovulation¹⁵. 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 PCOS¹³.
- **Recommendations**
- In anovulatory subfertile PCOS, women with associated male factor subfertility IUI is recommended along with OI.
- In anovulatory subfertile PCOS women with unsuccessful conception despite OI, IUI is recommended.

5.2 In-vitro fertilization

In-vitro fertilization is indicated with or without intracytoplasmic sperm injection in patients who fail to conceive with first line or second line treatments. In-vitro fertilization is appropriate in women with PCOS who do have associated pathologies such as in the case of tubal damage, severe endometriosis, and pre-implantation genetic diagnosis and male factor infertility¹⁶. Although pregnancy rates with IVF are up to 40% to 50% per cycle, in cases with fertility in general, the success of the procedure is significantly influenced by the women's age¹⁷.

.Recommendations

- 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)
- 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)
- 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)
- 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 development of at least three leading follicle ≥ 17 mm in size. (Grade B, EL 4)

6. 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. Luteal phase in women with PCOS is supported with progesterone, which can transform the uterine glands for secretions, increase the vascularity of endometrial lining, and stabilize the endometrium in preparation for embryo implantation¹⁸.

Recommendations

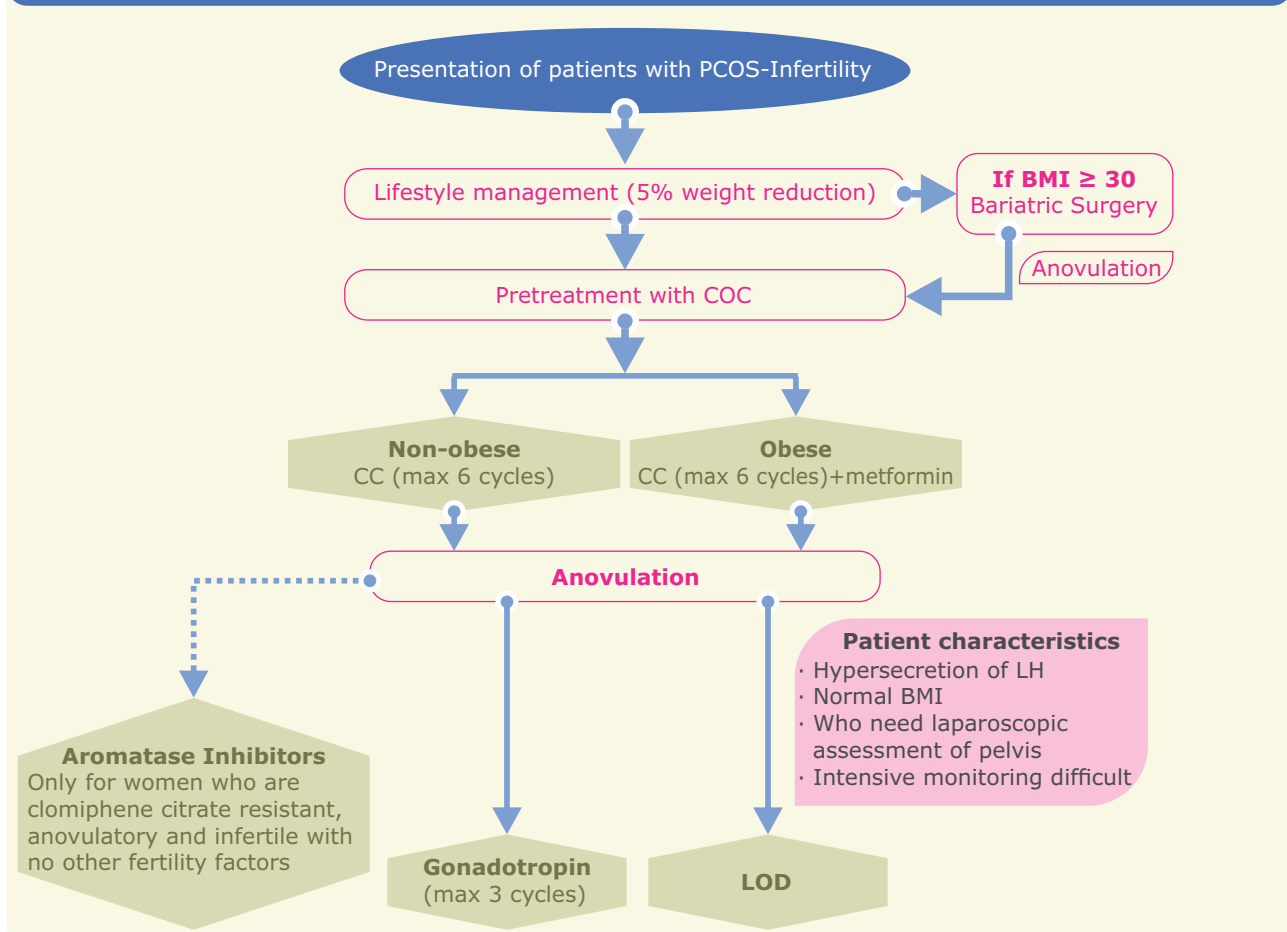
- Administration of luteal phase progesterone is recommended in subfertile PCOS women undergoing OI or assisted reproduction. (Grade A, EL 1)

References

1. Malik S, Jain K, Talwar P, Prasad S, Dhorepatil B, Devi G, et al. Management of polycystic ovary syndrome in India. *Fertil Sci Res* 2014;1:23-43.
2. Johansson J, Stener-Victorin E. Polycystic ovary syndrome: Effect and mechanisms of acupuncture for ovulation induction. *Evid Based Complement Alternat Med* 2013;2013:762615.
3. Dubey AK. Polycystic ovary syndrome: Diagnostic criteria and treatment in the anovulatory patient. In: Dubey AK, editor. *Infertility: Diagnosis Management and IVF*. 1st ed. New Delhi: Jaypee; 2012. p. 173-83.
4. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. *Clin Epidemiol* 2013;6:1-13.
5. Saoji AV. Primary infertility problem among female have been a source of concern in India lately. *Innov J Med Health Sci* 2014;4:332-40.
6. Berger JJ, Bates Jr GW. Optimal management of subfertility in polycystic ovary syndrome. *International journal of women's health*. 2014;6:613.
7. Kawwass JF, Loucks TL, Berga SL. An algorithm for treatment of infertile women with polycystic ovary syndrome. *Middle East Fertility Society Journal*. 2010;15(4):231-9.
8. De La Cruz-Muñoz N, Lopez-Mitnik G, Arheart KL, Miller TL, Lipshultz SE, Messiah SE. Effectiveness of bariatric surgery in reducing weight and body mass index among Hispanic adolescents. *Obesity surgery*. 2013;23(2):150-6.
9. Badawy A, Elnashar A. Treatment options for polycystic ovary syndrome. *Int J Womens Health*. 2011;3(1):25-35.
10. Shelly W, Draper MW, Krishnan V, Wong M, Jaffe RB. Selective estrogen receptor modulators: An update on recent clinical findings. *Obstet Gynecol Surv* 2008;63:163-81.
11. Kousta E, White DM, Franks S. Modern use of clomiphene citrate in induction of ovulation. *Hum Reprod Update* 1997;3:359-65.
12. DeUgarte CM, Bartolucci AA, Azziz R. Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment. *Fertil Steril* 2005;83:1454-60.
13. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. *Hum Reprod* 2008;23:462-77.
14. Mitra S, Nayak PK, Agrawal S. Laparoscopic ovarian drilling: an alternative but not the ultimate in the management of polycystic ovary syndrome. *Journal of Natural Science, Biology and Medicine*. 2015;6(1):40.
15. Cohlen BJ, Vandekerckhove P, te Velde ER, Habbema JD. Timed intercourse versus intra-uterine insemination with or without ovarian hyperstimulation for subfertility in men. *Cochrane Database Syst Rev* 2000;CD000360.
16. Homburg R. New concepts in the management of polycystic ovary syndrome. In: Gardner DK, Rizk BR, Falcone T, editors. *Human Assisted Reproductive Technology*. New York: Cambridge University Press; 2011. p. 110-8.
17. Liu K, Case A, Cheung AP, Sierra S, AlAsiri S, Carranza-Mamane B, Dwyer C, Graham J, Havelock J, Hemmings R, Lee F. Advanced reproductive age and fertility. *Journal of Obstetrics and Gynaecology Canada*. 2011;33(11):1165-75.
18. Shah D, Nagarajan N. Luteal insufficiency in first trimester. *Indian journal of endocrinology and metabolism*. 2013;17(1):44.

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Algorithm for the management of infertility associated with PCOS



IUI	IVF
<ul style="list-style-type: none"> For PCOS women with associated male factor subfertility intrauterine insemination For PCOS women with unsuccessful conception despite ovulation induction 	<ul style="list-style-type: none"> In subfertile PCOS women with no other causes of subfertility In PCOS women who fail to conceive or who have other indications for IVF
Luteal phase progesterone In subfertile PCOS women undergoing ovulation induction or assisted reproduction	

PCOS, Polycystic ovarian syndrome; BMI, Body Mass Index; COC, Combined oral contraceptive pills; CC, Clomiphene citrate; LH, Luteinizing hormone; LOD, Laparoscopic operative drilling; IUI, Intrauterine insemination; IVF, In-vitro fertilization.

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