

Managing Stimulation in Polycystic Ovary Syndrome

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ABSTRACT

About 70–80% of women with polycystic ovary syndrome (PCOS) exhibit anovulatory infertility as the primary cause of infertility. Ovulation induction can help these women to achieve a pregnancy. The objective of this review was to suggest a treatment approach for infertility in women with PCOS, for whom a multitude of treatment options exist. In women with PCOS, the importance of lifestyle modifications, diet, and weight loss should be stressed. Currently, letrozole is the first drug of choice in women with PCOS, owing to the better clinical outcomes. Additional first-line medical alternatives include metformin, inositol, melatonin, and gonadotropins. Other second and third-line treatment options are also available for the treatment of infertility in women with PCOS.

Key words: Infertility, Letrozole, Ovulation induction, Polycystic ovary syndrome

BACKGROUND

Polycystic ovary syndrome (PCOS) is a common endocrinological disorder in women of reproductive age causing infertility. About 70–80% of women with PCOS exhibit anovulatory infertility as the primary cause of infertility. For these women to achieve a pregnancy, it is important for ovulation to occur. There are two main treatment strategies involving similar medications for ovulation in PCOS as mentioned below:

- a. Ovulation Induction (OI): This treatment strategy is commonly used in patients who do not ovulate on their own. External stimulants are used for ovulation, resulting in monofolliculogenesis.
- b. Controlled Ovarian Stimulation: It is used in women who have regular ovulatory cycles but still experience infertility. This strategy results in multifolliculogenesis.

PHENOTYPIC CLASSIFICATION OF PCOS

The Rotterdam criteria define the classification of PCOS as mentioned in Table 1. It is divided into four phenotypes.

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A study by Reshef *et al.*, published in March 2020 highlights the clinical significance of Anti-Mullerian Hormone (AMH) levels as a diagnostic parameter in PCOS women. A lot of lean PCOS women with hyperandrogenism have high levels of AMH. Clinical AMH value of more than 8 ng/mL was found to be associated with a low birth rate. Hence, it is important to address the hyperandrogenism and the AMH values for these women to have a healthy pregnancy.

OI AGENTS

Letrozole

Clomiphene citrate (CC) has been the drug of choice for OI in PCOS for a long time. However, currently, letrozole is the first drug of choice in women with PCOS for better clinical outcomes. Table 2 suggests the different protocols available for the administration of letrozole in PCOS.

Franik *et al.*, in 2019, based on 42 randomized controlled trials in approximately 7935 women stated that letrozole resulted in a higher live birth rate in women with PCOS as compared to CC. However, the ovarian hyperstimulation rates were similar and there was no difference in the miscarriage and multiple pregnancy rates as compared to CC.

METFORMIN

Metformin can be considered as a reliable drug in PCOS management as an insulin-sensitizing agent. Morley *et al.*, in 2017

Table 1: Classification of various PCOS phenotypes

PCOS phenotypes	Definition	Includes
1	Classic PCOS	Women with polycystic ovarian morphology on ultrasound
2	Classic PCOS	Women with normal ovaries on ultrasound
3	Ovulatory PCOS	Symptoms of hyperandrogenism, polycystic ovarian morphology, and ovulatory cycles in women
4	Normoandrogenic PCOS	Women have chronic anovulation, polycystic ovarian morphology, and no clinical or biochemical signs of androgen excess or hyperandrogenism

Table 2: Letrozole dosing protocols

Dose and Duration	Uses
2.5 mg/day from cycle day 3 to 7	Used in patients with high AMH >5 ng/mL
5 mg/day from cycle day 3 to 7	Used in most of the PCOS patients Can be started on day 2 or 3
20 mg once on cycle day 3	Single dosing strategy using 20 mg at once This is not a popular strategy and is rarely used
2.5 mg from cycle day 1 to 10	Extended protocol for use beyond the regular 5-day treatment

demonstrated that metformin improved the menstrual pattern, ovulation rate, and the clinical pregnancy rates in PCOS women. Furthermore, the International PCOS guidelines released in 2018 by ESHRE, ASRM, etc., suggested that metformin can be added to the treatment plan for PCOS rather than persisting with CC or gonadotropins alone.

INOSITOL

The International PCOS Guidelines in 2018 stated that inositol can be used in PCOS, and evidence suggests that D-chiro inositol may improve ovulation rates, however, it does not have any effect on the body-mass index (BMI) or improves the metabolic syndrome in women with PCOS.

However, Deepti *et al.*, in May 2020 reported that 9 articles were reviewed on inositol usage in PCOS, and their use has showed improvement in the oocyte and embryo quality. More randomized controlled trials are required to prove its strong efficacy.

MELATONIN

Melatonin is usually administered when the egg quality is bad in women with PCOS. Sina *et al.*, showed that in PCOS patients, the serum levels of melatonin are high. However, the follicular level of melatonin remains decreased.

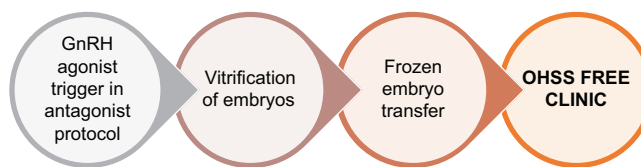


Figure 1: Segmentation approach to obtain an ovarian hyperstimulation syndrome-free clinic.

Melatonin is important to promote the oocyte maturation and ovulation by protecting the oocytes against oxidative stress. It also promotes weight loss, healthy BMI and reduces intra-abdominal fat. Supplementation of melatonin in PCOS women should be strongly considered.

GONADOTROPINS

These are the second-line drugs given in PCOS patients and the administration of gonadotropins requires ultrasound monitoring. They always present a risk of multiple pregnancies and hence, low dose gonadotropin protocols can induce a better monofollicular response as compared to CC or letrozole. In PCOS patients with CC resistance, it is recommended to use gonadotropins along with metformin for a better clinical response. Furthermore, trigger should be used only when <2 follicles are present.

The Cochrane review of 2015 consisting of 14 trials in 1726 women compared ten trials between recombinant follicle-stimulating hormone (FSH) versus urinary FSH and 4 trials between FSH-P versus HMG. It suggested that there was no difference in live birth or ovarian hyperstimulation rates between them. Hence, any choice of gonadotropin can be successfully used in PCOS women.

GONADOTROPIN STEP-UP DOSING PROTOCOL

1. Conventional step-up protocol A dose 75–150 IU of gonadotropins is started from day 1 to 5. The dose is increased by 75 IU FSH every 5 days until the desired follicular response is seen.
2. Chronic low dose step-up protocol A low starting dose of 37.5–75 IU is given 7 days. After 7 days, an ultrasound monitoring is performed, based on which the dose can be increased by 50–100% of the starting dose until the next 7 days. Human chorionic gonadotropin (hCG) 5000 IU can be used as a trigger for achieving a dominant follicle of >16 mm size.
3. Step-down protocol Started with dose of 112.5–187.5 IU/day and the dose is decreased every 4–5 days by 37.5 IU until a dominant follicle of >16mm is seen. hCG 5000 IU is used as a trigger.
4. Sequential regimen CC or letrozole is administered by cycle day 2–5. Gonadotropins at the dose of 75 IU are added from day 6. Ultrasound monitoring is done for observing the developing

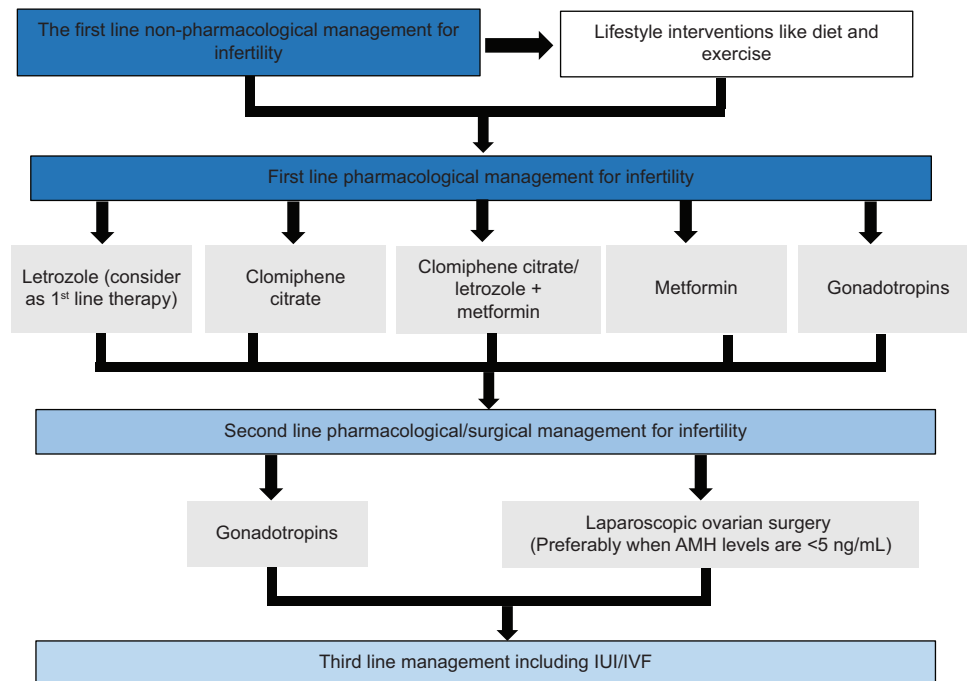


Figure 2: Treatment algorithm for infertility in polycystic ovary syndrome.

follicles and once the dominant follicle reached 17–18 mm, hCG trigger is administered.

GONADOTROPIN-RELEASING HORMONE (GNRH) ANTAGONISTS

GnRH antagonists are preferred to be added to the treatment regimen as they prevent premature luteinization in women with PCOS, leading to 25–30% higher pregnancy rates with IUI.

Trigger

A low dose hCG and GnRH analog are used as triggers. Sometimes, a dual trigger is also given, which includes a bolus of GnRH agonist for the release of luteinizing hormone (LH) and FSH from the pituitary along with the long-acting LH activity of a small bolus dose of hCG, covering the early luteal phase LH deficiency.^[1]

Plan of Action

The International PCOS guidelines recommend OI with timed intercourse as the first choice for achieving a pregnancy. The usual course of action for fertility treatment in PCOS patients includes:

- CC or letrozole therapy with timed intercourse – 3 cycles
- CC or letrozole + FSH + intrauterine insemination (IUI) – 2 cycles
- CC or letrozole + FSH + antagonist+ IUI – 2 cycles
- FSH + antagonist + IUI – 2 cycles
- *In vitro* fertilization (IVF)

Indications that suggest proceeding to IVF include poor or lack of response to OI, prevention of ovarian hyperstimulation,

or coincidental to other factors such as male or tubal factors or unexplained infertility.

IVF

IVF is the third line of management resulting in similar pregnancy rates for both PCOS and non-PCOS women. In this procedure, the GnRH antagonist protocol is preferred. Analog, low dose hCG, or dual trigger can be used in IVF procedure. Metformin is always preferred as an adjunct therapy during IVF.

Segmentation Approach

The most common problem encountered with the IVF procedure is the serious consequences of ovarian hyperstimulation syndrome (OHSS). In recent times, a segmentation approach^[2] to manage this in women with PCOS has been developed [Figure 1], leading to an OHSS free clinic.

Algorithm for the Management of Infertility in PCOS

The International guidelines recommended an algorithm for the treatment of infertility in PCOS outlined in Figure 2.^[3]

CONCLUSION

Women with PCOS often present with infertility. Initiating medications for OI is comparatively a simple treatment for female infertility. First-line management of infertility should always include lifestyle modifications such as diet and exercise.^[4] CC has been the drug of choice for OI in PCOS for a long time. However, currently, letrozole is the first drug of choice in women with

PCOS. Gonadotropins and laparoscopic ovarian surgery should be considered as second-line therapy for infertility. If a patient does not become pregnant in a timely manner, resources including IUI or IVF are other effective options.

REFERENCES

1. Kol S, Humaidan P. GnRH agonist triggering: Recent developments. *Reprod Biomed Online* 2013;26:226-30.
2. Available from: https://www.researchgate.net/publication/290168222_early_onset_ovarian_hyperstimulation_syndrome_despite_use_of_segmentation_approach_and_ovarian_hyperstimulation_syndrome_prophylaxis [Last accessed on 2022 Jan 18].
3. Jean Hailes for Women's Health. Resources, Jean Hailes; 2019. Available from: <https://www.jeanhailes.org.au/resources> [Last accessed on 2022 Jan 18].
4. Kite C, Lahart IM, Afzal I, Broom DR, Randeve H, Kyrou I, et al. Exercise, or exercise and diet for the management of polycystic ovary syndrome: a systematic review and meta-analysis. *Syst Rev* 2019;8:51.

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