

Ovulation Induction for PCOS Anovulatory Infertility

Key Points

- Infertility is the main clinical manifestation of ovulatory dysfunction in patients with PCOS.
- Weight reduction is the primary therapy in obese PCOS women as it increases response to ovulation induction agents, reduces pregnancy loss and obstetric complications related to obesity.
- Ovulation induction treatment should be carried out within the specialised Fertility team as one of the treatment options to couples referred to the Trust for fertility management.
- Letrozole is the first-line ovulation induction agent as recommended by the current evidence due to its higher pregnancy and live birth rates. However, it is not licensed for this indication.
- Clomiphene citrate (CC) has traditionally been the first-line ovulation induction agent and is the only drug that is licensed for this indication. It is going to be used as a second line as requires follicle tracking and has lower pregnancy rates than Letrozole.
- Laparoscopic ovarian drilling is recommended in PCOS women resistant to ovulation induction agents.

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Abbreviations

AMH	Anti-Müllerian hormone
BMI	Body mass index
CC	Clomiphene citrate
ICSI	Intracytoplasmic sperm injection
IVF	In vitro fertilisation
LOD	Laparoscopic ovarian drilling
OHSS	Ovarian hyperstimulation syndrome
OI	Ovulation induction
PCOS	Polycystic ovary syndrome

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1. Introduction

Polycystic ovary syndrome (PCOS) is a group of heterogeneous endocrine disorders affecting women characterized by oligo-anovulation, hyperandrogenism, and polycystic ovarian morphology (in either or both ovaries) on transvaginal ultrasound. The prevalence is between 8.5 and 20% depending on the criteria used for the diagnosis of the condition. Infertility is the main clinical manifestation of ovulatory dysfunction in patients with PCOS.

2. Weight Reduction

The ESHRE (*International Evidence-Based Guideline for the Assessment and Management of Polycystic Ovary Syndrome 2023*) recommends that weight loss is the primary therapy in PCOS. Obesity is linked to anovulation and pregnancy loss as well as poor response to ovulation induction agent (e.g. Clomiphene citrate) and ovarian drilling¹⁻⁶. Weight loss as little as 5–10% of bodyweight can restore ovulation and improve response to ovulation induction medications^{3,7}. A referral to a dietician should be considered in the holistic management of the patient. Healthy lifestyle behaviours (healthy eating and regular physical activity) should be recommended in all women with PCOS to achieve and/or maintain healthy weight, to optimise health, and quality of life. Certain ethnic groups at high cardio-metabolic risk require more consideration.

Pharmacologic anti-obesity agents should be considered an experimental therapy for women with PCOS for the purpose of improving fertility, with risk to benefit ratios currently too uncertain to advocate this as fertility therapy⁸.

Bariatric surgery should be considered as an experimental therapy in women with PCOS for the purpose of having healthy baby, with risk to benefit ratios currently too uncertain to advocate this as fertility therapy⁸.

3. Pharmacologic agents and ovulation induction

Ovulation induction treatment should be carried out within the specialised Fertility team.

Letrozole

Letrozole is now recommended as the first line treatment for ovulation induction (as stated in the ESHRE guidelines) because of its higher pregnancy and live birth rates when compared to Clomiphene citrate⁸. However, it is only licensed as an adjuvant treatment for breast cancer in post-menopausal women. Currently, a verbal consent is required from all patients before Letrozole is prescribed for ovulation induction treatment.

Women should be advised that pregnancy rates are 40-60% higher with Letrozole compared to Clomiphene with reduced risk of multiple pregnancy, 3.7% vs 5-7% respectively. Studies show that the risk of miscarriage is lower with Letrozole group^{9,11}. Initial dose of Letrozole is 2.5 mg once a day from day 2 to day 6 (D2-D6) of the menstrual cycle. This can be increased to 5 mg and subsequently to 7.5 mg if no response is achieved. The patient should be informed that its cumulative ovulation rate is higher than that with Clomiphene citrate; 61.7% for up to five cycles in comparison with 48.3%^{8,9,10}, with more cumulative live birth rates of 27.5% vs. 19.1% respectively.

Clomiphene citrate

Clomiphene citrate (CC) has traditionally been the first-line ovulation induction agent and is the only ovulation induction drug that is licensed for this indication. The initial dose is 50 mg once a day from D2-D6 of the menstrual cycle. The dose can be increased to 100 mg and subsequently 150 mg a day if no response is achieved. A recent meta-analysis of RCT-s found CC to be inferior to Letrozole^{9,10-12}. This is thought to be due to its anti-estrogenic effects on the endometrium, cervical mucus, and accumulation in tissues leading to prolonged depletion of estrogen receptors. In case of CC resistance (no ovulation) these patients will require other forms of ovulation induction.

Metformin

Metformin is a weak ovulation induction agent. Its use for ovulation induction is not licensed. It assists in weight reduction and its effect is better in obese women with PCOS (BMI>30). Usual doses of metformin range from 1000mg to 3000 mg a day. Studies have found an improved ovulation and pregnancy rate per participant with the use of metformin plus CC^{12,13}. Metformin may be associated with mild gastrointestinal related side effects. It can be continued until 12 weeks when the pregnancy is achieved.

Gonadotropins

Gonadotrophins are a second line pharmacological agent in women with PCOS who have failed first line oral ovulation induction therapy and are anovulatory with no other infertility factors. Gonadotrophin treatment is not currently offered in Frimley Health due to their high cost, requirement of intensive ultrasound monitoring and the risks and implications of potential multiple pregnancy.

Laparoscopic Ovarian Drilling (LOD)

LOD should be a second line therapy for women with PCOS who are resistant to CC or Letrozole⁸. LOD could potentially be offered as first line treatment if laparoscopy is indicated for another reason⁸.

Risks should be explained to all women with PCOS considering laparoscopic ovarian surgery. They include:

- intra-operative and post-operative risks that are higher in women who are overweight and obese. For this reason, laparoscopy for ovarian drilling alone should NOT be offered to women with BMI above 30.
- there may be a small associated risk of lower ovarian reserve or loss of ovarian function; counselling will consider the baseline AMH level, which is usually high in this group.
- risk of formation of peri-ovarian adhesions.

4. Assessment of factors that may affect fertility, treatment response or pregnancy outcomes

Factors such as weight, blood pressure, blood glucose, smoking, alcohol, diet, exercise, sleep and mental, emotional and sexual health should be optimised in women with PCOS, to improve reproductive and obstetric outcomes, aligned with NHS Public Health recommendations for the general population.

Health care professionals should refer to the NICE and RCOG guidelines for the management of polycystic ovary syndrome available at <https://cks.nice.org.uk/polycystic-ovary-syndrome> and <https://www.rcoq.org.uk/en/guidelines-research-services/guidelines/gtg33>.

Women with BMI more than 30 should be advised that weight loss is a **primary therapy** for PCOS and should be given their target weight to achieve this goal.

Ovulation induction should be offered to women with BMI<30 (preferably BMI<25) or, in exceptional circumstances, in women with BMI 30-35 if they have already achieved a significant weight loss. This is to achieve a healthy pregnancy and for reasons detailed above.

5. Investigations

All women with oligo-anovulation should have Prolactin and Free Androgen Index checked in addition to the routine fertility investigations: Baseline (D2-D5) FSH, LH, E2, TSH and Rubella IgG. The male partner should have a semen analysis performed before OI is offered; if there is severe male factor OI is not appropriate as IVF with ICSI would be recommended.

All women should have a baseline transvaginal pelvic ultrasound in the preceding 3 months prior to commencing OI therapy.

AMH is not a necessary first line investigation in women with PCOS and should be reserved for women that are referred to IVF/ICSI treatment as it is a prognostic factor for the risk of OHSS⁸. However, clinical judgement should be used for its use in complex cases and prior to ovarian surgery.

For women with PCOS and infertility due to anovulation alone with normal semen analysis and low risk of tubal pathology, ovulation induction can be commenced without the need for tubal patency test⁸.

At **Wexham** site, it has been agreed that if patient is low risk for tubal disease and anovulation is the main problem, 3 cycles of ovulation induction treatment can be tried prior to tubal testing. After 3 unsuccessful cycles of ovulation induction, tubal assessment test should be arranged.

This practice differs at **Frimley** site, where all women get a HYCOSY test to check tubal patency on entry to the fertility service arranged by the Fertility nurse.

Tubal patency testing with HSG should be considered prior to ovulation induction for women with PCOS at high risk of tubal factor infertility (previous ectopic pregnancy, previous major abdominal surgery, previous pelvic inflammatory disease, history of endometriosis)⁸. In some cases where the couple have already tried for more than 12 months and time is critical, such as referral for NHS IVF, tubal testing can be used earlier in the timeline.

Glucose tolerance test should be arranged in pregnancy in women with PCOS, given increased risk of adverse maternal and offspring outcomes.

6. Ovulation Induction Operational Procedure

(Please note: ovulation induction with follicle tracking is offered only when clomiphene citrate is used)

All patients should receive a patient information leaflet (PIL) explaining the treatment of ovulation induction. Due to the risk of multiple pregnancy with CC, all patients should undergo follicle tracking in the first cycle to ensure mono or bi-follicular development only. If increased dosage is required, then further tracking is needed.

Letrozole - The initial dose of letrozole is 2.5 mg once a day taken D2-D6 of the menstrual cycle and a mid-luteal progesterone is requested. Patients are advised to call the fertility nurse at FPH or the fertility secretary at WPH for the result. In case of no ovulation the dose can be increased to 5 mg and then 7.5 mg which is the maximal dose.

Clomiphene

FPH does not offer follicle tracking service.

On D1 of her period, the patient calls the fertility secretary on 03006159812 (for WPH only) and books an appointment for follicle tracking on D11-D14. (the reason for this is that it will be difficult to meet this target of 2 days, we need a range due to few slots) of the cycle. CC 50mg should be commenced

on D2 of the menstrual cycle and taken once a day for five days (D2-D6). In case of oligo-amenorrhoea, withdrawal bleeding can be induced with medroxyprogesterone acetate [Provera®] 10 mg once a day for 5 days. Pregnancy should be excluded prior to this by performing a urinary pregnancy test at home.

The patient should be advised NOT to have unprotected intercourse before the first follicle tracking scan to avoid the risk of multiple pregnancy.

If there are less than three follicles >18 mm in size, the patient is advised to have intercourse. If none of the follicles has reached mean diameter of 18 mm, a follow up scan is required in 3 -4 days. If the follicles reach 18 mm, then a mid-luteal progesterone is requested. Patients are advised to contact the fertility secretary at WPH for the result and they are informed of further plan by the fertility team.

if 3 or more follicles > 18mm in size, the patient is advised to avoid intercourse in that cycle.

If no dominant follicle is achieved, anovulation is confirmed. Patient is advised to increase the CC to 100 mg once a day on D2-D6 of the subsequent cycle and the above procedure is followed. In exceptional circumstances, CC can be increased to 150mg once a day on D2-D6. A follow up appointment should be offered if pregnancy is not achieved after 3 ovulatory cycles on CC. This would be to discuss tubal patency testing in those who have not yet had it and other clinical factors.

Prolonged use of ovulation induction agents for more than 6 months should be avoided, due to poor success rates. This is in line with the national recommendations. However clinical factors can be used to individualise treatment plans in certain cases.

7. Risks associated with ovulation induction agents

- Multiple pregnancy. Clomiphene citrate OI is associated with 5-7% risk of twin pregnancy vs. 3.4% for Letrozole OI. The risk of triplets with clomiphene is 0.3%¹⁴.
- Ovarian hyperstimulation syndrome (OHSS). Risk of OHSS with clomiphene is less than 1%¹⁴. The risk with Letrozole is extremely rare. The symptoms of OHSS are abdominal discomfort, bloating, nausea and inability to pass urine. This is usually diagnosed on TVS as part of the follicle tracking. Patients should be advised NOT to have unprotected intercourse in this cycle in order to avoid the risk of multiple pregnancy. The ovulation induction agent should be restarted at a lower dose in the next cycle.
- The side effects associated with both Letrozole and CC include hot flushes, fatigue and dizziness, headaches, muscle aches and blurred vision^{10,15}.
- Multiple case series¹⁶⁻¹⁹ and multi-centre RCTs^{10,20} failed to note an increased risk of congenital anomalies with the use of Letrozole or CC (the baseline rate of congenital anomalies in the population is 5-8%²¹).
- The potential for borderline increased risk of ovarian tumours with 12 cycles or more has been noted²².

8. Cycle cancellation

Cycles may be cancelled for the following reasons:

- if 3 or more follicles > 18mm in size, the patient is advised to avoid intercourse in that cycle.
- Non-response to treatment: Approximately 30% of patients do not respond to the initial dose of treatment. If this happens, patients will restart the treatment on a higher dose. They can have metformin added to the treatment as there is some evidence that it would be beneficial.
- Over-response to treatment (See OHSS section above)
- Premature ovulation: Occasionally follicles ovulate earlier than expected i.e. at a smaller size, or sometimes they mature quicker than average. If this happens, the patient needs to be monitored with earlier scans in future cycles.

9. Follow up appointments

If pregnancy is not achieved after 6 months of ovulation induction treatment cycles, couples should be booked for a follow up appointment and a discussion for referral to IVF/ICSI treatment. In certain circumstances (advanced female age, low AMH, long duration of infertility, male factor), it is appropriate to offer referral for an IVF/ICSI treatment before completing six months of ovulation induction.

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Full version control record

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Related Documents

None.