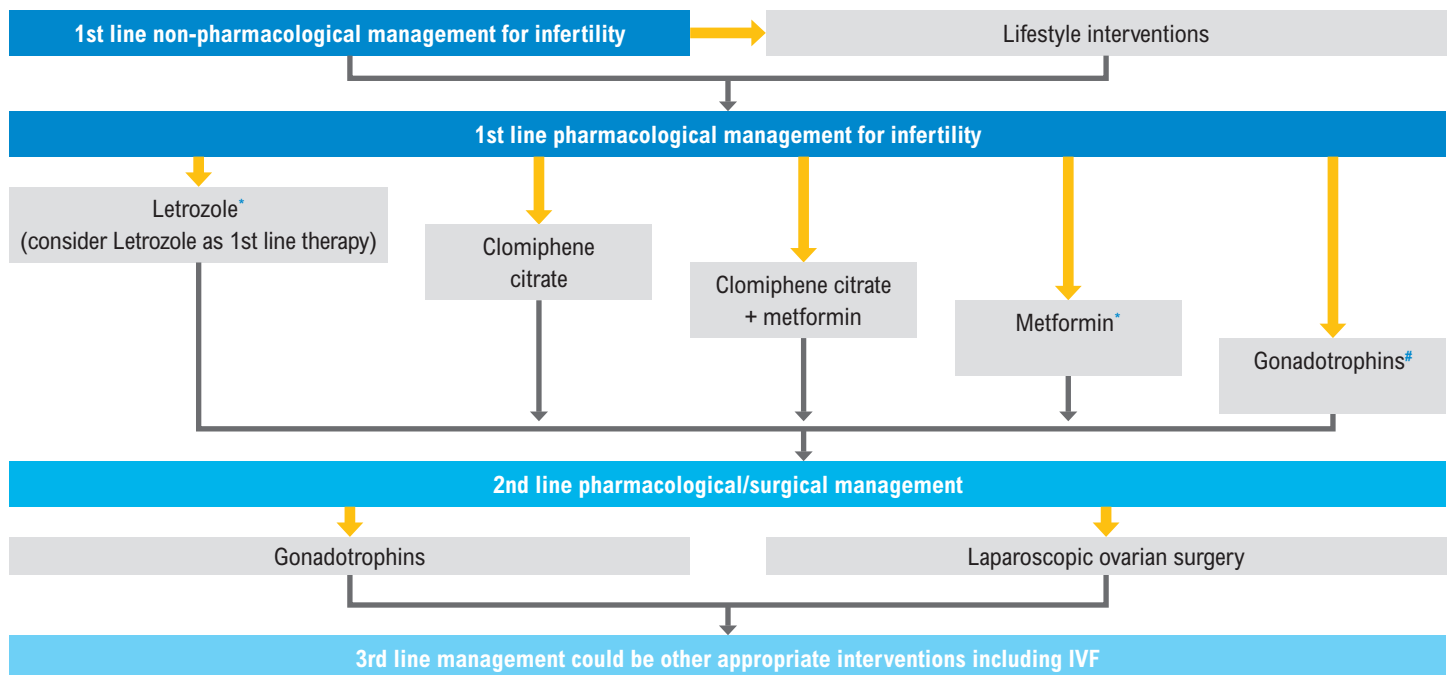


# Algorithm 5: Assessment and treatment of infertility



\* **Off label prescribing:** Letrozole, COCPs, metformin and other pharmacological treatments are generally off label in PCOS, as pharmaceutical companies have not applied for approval in PCOS. However, off label use is predominantly evidence-based and is allowed in many countries. Where it is allowed, health professionals should inform women and discuss the evidence, possible concerns and side effects of treatment.

## Assessment and treatment of infertility

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

Factors such as blood glucose, weight, blood pressure, 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 recommendations in the general population.

Refer to the International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018 available at: [www.monash.edu/medicine/sphpm/mchri/pcos](http://www.monash.edu/medicine/sphpm/mchri/pcos)

Monitoring during pregnancy is important for women with PCOS, given increased risk of adverse maternal and offspring outcomes.

For women with PCOS and infertility due to anovulation alone with normal semen analysis, the risks, benefits, costs and timing of tubal patency testing should be discussed on an individual basis.

Tubal patency testing should be considered prior to ovulation induction for women with PCOS where there is suspected tubal infertility.

### Ovulation induction principles

The use of ovulation induction agents, including letrozole, metformin and clomiphene citrate is off label in many countries\*.

Pregnancy should be excluded prior to ovulation induction.

Unsuccessful, prolonged use of ovulation induction agents should be avoided, due to poor success rates.

### Letrozole

Letrozole should be considered first line pharmacological treatment for ovulation induction in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation, pregnancy and live birth rates.

Where letrozole is not available or use is not permitted or cost is prohibitive, health professionals should use other ovulation induction agents.

Health professionals and women should be aware that the risk of multiple pregnancy appears to be less with letrozole, compared to clomiphene citrate.

### Clomiphene citrate and metformin

Clomiphene citrate could be used alone in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and pregnancy rates.

Metformin could be used alone in women with PCOS, with anovulatory infertility and no other infertility factors, to improve ovulation, pregnancy and live birth rates, although women should be informed that there are more effective ovulation induction agents.

Clomiphene citrate could be used in preference, when considering clomiphene citrate or metformin for ovulation induction in women with PCOS who are obese (BMI is  $\geq 30$  kg/m<sup>2</sup>) with anovulatory infertility and no other infertility factors.

If metformin is being used for ovulation induction in women with PCOS who are obese (BMI  $\geq 30$ kg/m<sup>2</sup>) with anovulatory infertility and no other infertility factors, clomiphene citrate could be added to improve ovulation, pregnancy and live birth rates.

Clomiphene citrate could be combined with metformin, rather than persisting with clomiphene citrate alone, in women with PCOS who are clomiphene citrate-resistant, with anovulatory infertility and no other infertility factors, to improve ovulation and pregnancy rates.

The risk of multiple pregnancy is increased with clomiphene citrate use and therefore monitoring needs to be considered.

## Gonadotrophins

Gonadotrophins could be used as second line pharmacological agents in women with PCOS who have failed first line oral ovulation induction therapy and are anovulatory and infertile, with no other infertility factors.

# Gonadotrophins could be considered as first line treatment, in the presence of ultrasound monitoring, following counselling on cost and potential risk of multiple pregnancy, in women with PCOS with anovulatory infertility and no other infertility factors.

Gonadotrophins, where available and affordable, should be used in preference to clomiphene citrate combined with metformin therapy for ovulation induction, in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates.

Gonadotrophins with the addition of metformin, could be used rather than gonadotrophins alone, in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, to improve ovulation, pregnancy and live birth rates.

Either gonadotrophins or laparoscopic ovarian surgery could be used in women with PCOS with anovulatory infertility, clomiphene citrate-resistance and no other infertility factors, following counselling on benefits and risks of each therapy.

Where gonadotrophins are prescribed, the following should be considered:

- cost and availability
- expertise required for use in ovulation induction
- degree of intensive ultrasound monitoring required
- lack of difference in clinical efficacy of available gonadotrophin preparations
- low dose gonadotrophin protocols optimise monofollicular development
- risk and implications of potential multiple pregnancy

Gonadotrophin induced ovulation should only be triggered when there are fewer than three mature follicles and should be cancelled if there are more than two mature follicles with the patient advised to avoid unprotected intercourse.

## Anti-obesity agents

Pharmacological 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 therapy.

## Laparoscopic ovarian surgery

Laparoscopic ovarian surgery could be second line therapy for women with PCOS, who are clomiphene citrate resistant, with anovulatory infertility and no other infertility factors.

Laparoscopic ovarian surgery could potentially be offered as first line treatment if laparoscopy is indicated for another reason in women with PCOS with anovulatory infertility and no other infertility factors.

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

Where laparoscopic ovarian surgery is to be recommended, the following should be considered:

- comparative cost
- expertise required for use in ovulation induction
- intra-operative and post-operative risks are higher in women who are overweight and obese
- there may be a small associated risk of lower ovarian reserve or loss of ovarian function
- periadnexal adhesion formation may be an associated risk

## Bariatric Surgery

Bariatric surgery should be considered 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 therapy.

If bariatric surgery is to be prescribed, the following should be considered:

- comparative cost
- the need for a structured weight management program involving diet, physical activity and interventions to improve psychological, musculoskeletal and cardiovascular health to continue post-operatively
- perinatal risks such as small for gestational age, premature delivery, possibly increased infant mortality
- potential benefits such as reduced incidence of large for gestational age fetus and gestational diabetes
- recommendations for pregnancy avoidance during periods of rapid weight loss and for at least 12 months after bariatric surgery with appropriate contraception

If pregnancy occurs, the following should be considered:

- awareness and preventative management of pre- and post-operative nutritional deficiencies is important, ideally in a specialist interdisciplinary care setting
- monitoring of fetal growth during pregnancy

## In-vitro fertilisation (IVF)

In the absence of an absolute indication for IVF ± ICSI, women with PCOS and anovulatory infertility could be offered IVF third line where other ovulation induction therapies have failed.

In women with anovulatory PCOS, the use of IVF is effective and when elective single embryo transfer is used, multiple pregnancies can be minimised.

Women with PCOS undergoing IVF ± ICSI therapy should be counselled prior to starting treatment, including on:

- availability, cost and convenience
- increased risk of ovarian hyperstimulation syndrome
- options to reduce the risk of ovarian hyperstimulation

Urinary or recombinant follicle stimulation hormone can be used in women with PCOS undergoing controlled ovarian hyperstimulation for IVF ± ICSI, with insufficient evidence to recommend specific FSH preparations.

Exogenous recombinant luteinising hormone treatment should not be routinely used in combination with follicle stimulating hormone therapy in women with PCOS undergoing controlled ovarian hyperstimulation for IVF ± ICSI.

A gonadotrophin releasing hormone antagonist protocol is preferred in women with PCOS undergoing an IVF ± ICSI cycle, over a gonadotrophin releasing hormone agonist long protocol, to reduce the duration of stimulation, total gonadotrophin dose and incidence of ovarian hyperstimulation syndrome (OHSS).

Human chorionic gonadotrophins should be used at the lowest doses to trigger final oocyte maturation in women with PCOS undergoing an IVF ± ICSI cycle to reduce the incidence of OHSS.

Triggering final oocyte maturation with a GnRH agonist and freezing all suitable embryos could be considered in women with PCOS having an IVF/ICSI cycle with a GnRH antagonist protocol and at an increased risk of developing OHSS or where fresh embryo transfer is not planned.

In IVF ± ICSI cycles in women with PCOS, consideration should be given to an elective freeze of all embryos.

Adjunct metformin therapy could be used before and/or during follicle stimulating hormone ovarian stimulation in women with PCOS undergoing IVF ± ICSI therapy with a gonadotrophin releasing hormone agonist protocol, to improve the clinical pregnancy rate and reduce the risk of OHSS.

In a gonadotrophin releasing hormone agonist protocol with adjunct metformin therapy, in women with PCOS undergoing IVF ± ICSI treatment, the following could be considered:

- metformin commencement at the start of gonadotrophin releasing hormone agonist treatment
- metformin use at a dose of between 1000mg to 2550mg daily
- metformin cessation at the time of the pregnancy test or menses (unless the metformin therapy is otherwise indicated)
- metformin side-effects (refer to the International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018 available at: [www.monash.edu/medicine/sphpm/mchri/pcos](http://www.monash.edu/medicine/sphpm/mchri/pcos))

In IVF ± ICSI cycles, women with PCOS could be counselled on potential benefits of adjunct metformin in a gonadotrophin releasing hormone antagonist protocol to reduce risk of ovarian hyperstimulation syndrome (refer to the International evidence-based guideline for the assessment and management of polycystic ovary syndrome 2018 available at: [www.monash.edu/medicine/sphpm/mchri/pcos](http://www.monash.edu/medicine/sphpm/mchri/pcos)).

The term in vitro maturation (IVM) treatment cycle should be applied to “the maturation in vitro of immature cumulus oocyte complexes collected from antral follicles” (encompassing both stimulated and unstimulated cycles, but without the use of a human gonadotrophin trigger).

In units with sufficient expertise, IVM could be offered to achieve pregnancy and live birth rates approaching those of standard IVF ± ICSI treatment without the risk of OHSS for women with PCOS, where an embryo is generated, then vitrified and thawed and transferred in a subsequent cycle.