Infertility management in women with polycystic ovary syndrome: a review
Anita Cunha, MDa,*, Ana Margarida Póvoa, MD, PhDb,c,d

Abstract
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women and a major cause of anovulatory infertility. Various medical options are used, alone or in combination, to treat subfertility associated with polycystic ovary syndrome. This narrative review was conducted to provide an update and summarize the available evidence on the management of polycystic ovary syndrome related infertility. A wide literature search was performed and preferably randomized controlled trials and systematic reviews were included. Management is often centered on lifestyle changes. Pharmacological ovulation induction is the next step, with recommended use of letrozole, clomiphene citrate or gonadotropins. When it fails, assisted reproductive technologies or laparoscopic ovarian drilling are frequently advised. Combination treatment with metformin is often recommended. More recent alternative and adjunctive treatments have been suggested, like inositol, vitamin D, bariatric surgery and acupuncture, but further research is needed for recommendation.

Keywords: assisted, female, infertility, metformin, ovulation induction, polycystic ovary syndrome, reproductive techniques

Introduction
Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women, with an overall prevalence of 5% to 15%, and a frequent cause of infertility.1,2

Currently, the diagnosis is based on the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine criteria, also known as Rotterdam criteria, from 2003.3 The patient must meet 2 out of 3 of the following criteria: I, oligo/anovulation; II, clinical (hirsutism, acne, male pattern alopecia) or biochemical signs of hyperandrogenism (raised serum testosterone levels); III, polycystic ovaries, that consist in 12 or more follicles measuring 2 to 9 mm in diameter or increased ovarian volume, over 10 cm3, on transvaginal ultrasound examination. Exclusion of other etiologies of menstrual disturbance and hyperandrogenism is mandatory.3

It is hypothesized that PCOS results from a vicious circle of androgen excess favoring abdominal and visceral adipose tissue deposition, that induces insulin resistance (IR) and compensatory hyperinsulinemia, further facilitating androgen secretion by the ovaries and adrenal glands.4 This cyclical pathogenic interaction between IR, hyperinsulinemia, and hyperandrogenism, in combination with hypothalamic-pituitary dysfunction, leads to further ovarian dysfunction that can result in anovulation and infertility.4

Ovulation disorders are the cause of infertility in around 25% of couples and PCOS is the major cause of anovulatory infertility, accounting for approximately 70% of all cases.1–7 A range of endocrine and metabolic traits are also associated with PCOS and these include obesity, dyslipidemia, IR, hyperinsulinism and an increased risk of type 2 diabetes mellitus and cardiovascular disease. Women with PCOS may also have an increased risk of miscarriage and pregnancy complications such as gestational diabetes.8,9

Management of subfertility associated with PCOS is often centered on lifestyle changes, pharmacotherapy, surgical treatment and assisted reproductive technologies (ART). Recent alternative and adjunctive treatments have been used, and changes to the treatment algorithm have been suggested.10

This narrative review was conducted to provide an update and summarize the available evidence on the management of PCOS related infertility.

Material and methods
A literature search was performed on PubMed, Web of Science, Scopus and Cochrane Library, using the keywords PCOS, anovulation, infertility, and treatment/management/therapy. Relevant clinical guidelines were also searched. No language restrictions were applied. Preferably, randomized controlled trials and systematic reviews including randomized controlled trials and/or cohort studies were included. The latest search was completed on January 15, 2020.

Management of PCOS related infertility

Lifestyle changes
Lifestyle changes, promoting weight loss, are the first-line treatment recommended for women with PCOS (clinical
consensus strong recommendation). It is known that a healthy diet and regular physical activity help to reduce IR and hyperandrogenism, and to optimize hormonal imbalance, lipid profile and cardiovascular health.11,12

When it comes to fertility outcomes, there is no robust evidence on the lifestyle changes impact. Some studies state that weight loss in overweight infertile women with PCOS can be associated with sporadic ovulation and better response to ovulation induction treatments with an increase in pregnancy and live birth rates.5,14 A study showed that a reduction in weight of as little as 5% from initial body weight could restore regular menses and improve response to ovulation-inducing and fertility medications.13 In addition, Hakimi and Cameron propose that consistent physical activity, via modulation of the hypothalamic-pituitary-gonadal axis, can improve fertility outcomes.16

There are currently no specific diet type recommendations for women with PCOS, but an energy deficit of 30% or 500 to 750 kcal/d (1200–1500 kcal/d) could be prescribed.10 General recommendations on exercise include minimum of 150 min/wk of moderate intensity physical activity or 75 min/wk vigorous intensity and muscle strengthening activities on 2 nonconsecutive days per week.10 For modest weight loss, prevention of weight regain and greater health benefits, a minimum of 250 min/wk of moderate intensity activities or 150 min/wk of vigorous intensity and muscle strengthening activities on 2 nonconsecutive days per week is recommended.10 The effectiveness of lifestyle interventions is likely to be improved when including behavioral strategies such as goal setting, self-monitoring, cognitive restructuring, problem solving, and relapse prevention strategies.10,17

**Ovulation induction**

Since 70% of women with PCOS have anovulation or oligo-ovulation, ovulation induction is the cornerstone for treatment of women with PCOS suffering from infertility.

In women with PCOS and infertility due to anovulation alone with normal semen analysis, tubal patency testing, by hysterosalpingography or hysterosonosalpingography, should be considered prior to ovulation induction in women where there is suspected tubal infertility.10 Tubal pathology is a causative factor in 20% of subfertile couples.18 The WHO evidence report on infertility treatment in PCOS considers the assessment of tubal patency in infertility workup.19

Next, we present the most frequently used drugs for ovulation induction: letrozole, clomiphene citrate (CC), and gonadotropins.

**Selective estrogen receptor modulators (SERMs)—clomiphene citrate (CC).** Clomiphene citrate is a selective estrogen receptor modulator (SERM) considered, for many years, the first choice of treatment for ovulation induction in women with PCOS. CC acts as an anti-estrogen, blocking the estrogen receptors at the hypothalamus, which results in an increase in gonadotropin-releasing hormone (GnRH) pulse amplitude, and subsequently increased anterior pituitary production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), thereby stimulating the final maturation of follicles (Fig. 1).20

The anti-estrogenic effect can as well affect the endometrium and cervical mucus, with endometrial proliferation suppression, thus potentially inhibiting implantation.20 CC side effects include hot flushes, nausea, breast tenderness, dizziness and blurred vision.21 Standard treatment is usually a dose of 50 mg/d for 5 days, starting on day 2 to 5 of the cycle.21

CC induces ovulation in 70% to 90% of patients, but pregnancy rate is lower (30%–40%).22 Kafy and Tulandi described an increased twin pregnancy and triplets with CC (5%–7% and 0.3%, respectively), therefore monitoring with ultrasound to detect multifollicular development should be performed.23

Roughly 15% of PCOS patients do not respond to treatment.24 If ovulation is not achieved after 2 cycles, the dose can be gradually increased to 100 to 250 mg/d.21 If ovulation still does not occur, CC resistance is documented.24 Risk factors for resistance include obesity, IR and hyperandrogenemia.25

**Figure 1.** Mechanism of action of clomiphene citrate. Clomiphene citrate blocks the estrogen receptors at the hypothalamus, which results in an increase in GnRH pulse amplitude that leads to increased and prolonged FSH and LH secretion, stimulating the final maturation of follicles. ER = estrogen receptor, FSH = follicle-stimulating hormone, GnRH = gonadotropin-releasing hormone, LH = luteinizing hormone.
Current evidence-based guidelines propose the use of CC, as a second-line therapy, in women with PCOS with anovulatory infertility and no other infertility factors to improve ovulation and pregnancy rates (evidence-based conditional recommendation, very low quality of evidence).\textsuperscript{10}

In women with PCOS who are CC-resistant, CC could be combined with metformin (evidence-based conditional recommendation, moderate quality of evidence).\textsuperscript{10} Combined therapy may have a useful role, suggested by a recent Cochrane review by Morley et al, that found an improved clinical pregnancy and ovulation rate with metformin and CC versus CC alone, despite no significant difference between the groups in live birth rates.\textsuperscript{26}

Aromatase inhibitors (AI)—letrozole. The enzyme aromatase is responsible for androgen-to-estrogen conversion. Letrozole is the most used selective non-steroidal third-generation AI for ovulation induction.\textsuperscript{27} Letrozole suppresses ovarian estradiol secretion. Due to release from negative feedback on the hypothalamus, and temporary increase of intraovarian androgens, an increase in pituitary secretion of FSH, and follicular sensitivity to FSH occur, with subsequent improved ovulatory rates (Fig. 2).\textsuperscript{28}

Letrozole has relatively short half-life (approximately 45 hours) compared to CC, so adverse effects on estrogen target tissues are not expected.\textsuperscript{29}

Effective use of letrozole for ovulation induction, in women with an inadequate response to CC, was first described by Mitwall and Casper in 2001.\textsuperscript{29} A recent Cochrane review, by Franik et al, based on moderate-quality evidence, found higher live birth rates with letrozole compared to CC, and based on high-quality evidence, also found similar ovarian hyperstimulation syndrome (OHSS) rates with letrozole or CC, and no difference for miscarriage or multiple pregnancy.\textsuperscript{30} Also, the risk of multiple pregnancy appears to be less with letrozole, compared to CC for its highest mono-follicular growth rate.\textsuperscript{31}

Standard treatment is usually a dose of 2.5 mg/d for 5 days, starting on day 2 to 5 of a cycle (spontaneous or progestin-induced).\textsuperscript{32} Ovulation is monitored by ultrasound follicle tracking.\textsuperscript{32} When the leading follicle reaches at least 18 mm, ovulation can be triggered with human chorionic gonadotropin (hCG) and followed by timed intercourse.\textsuperscript{32} Ovulation is expected to occur 36 to 48 hours after trigger. Couples should be advised to avoid unprotected intercourse if there are more than

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**Figure 2.** Mechanism of action of letrozole. Letrozole inhibits androgen-to-estrogen conversion. Consecutively, the hypothalamic-pituitary axis is released from estrogenic negative feedback resulting in an increase in pituitary secretion of FSH with subsequent improved ovulatory rates. Also, increase in intraovarian androgens enhances follicular sensitivity to FSH. ER = estrogen receptor, FSH = follicle-stimulating hormone, GnRH = gonadotropin-releasing hormone, LH = luteinizing hormone.
Gonadotropins. In recent international guidelines, gonadotropin therapy for ovulation induction in anovulatory PCOS women continues to be recommended as a second-line option in women who have failed first line oral ovulation induction therapy, including AIs and SERMs (evidence-based conditional recommendation, low quality of evidence).10

In PCOS patients, gonadotropins are associated with a higher risk of OHSS and multiple pregnancies so they should only be used by clinicians having the requisite training and experience. Exogenous FSH stimulates proliferation of granulosa cells and follicular growth. The goal is to promote the growth and development of a single follicle. Different gonadotropin preparations, FSH or human menopausal gonadotropin appear to be equally effective, with no significant difference in live birth rate, clinical pregnancy rate, multiple pregnancy rate, miscarriage rate or OHSS incidence.33,34

To prevent hyperstimulation and minimize multifollicular development, low-dose step-up or a step-down protocols are preferred.10 In the low-dose step-up protocol, low initial doses of gonadotropins are used, after a menses, starting with 37.5 to 75IU/d, and increasing in small increments 25 to 37.5 IU after 7 days or more if no follicle ≥10mm has developed. Ultrasonography provides measurement of follicular development and generally should be performed after the first 4 to 5 days of treatment and at subsequent intervals of 1 to 3 days according to response. Although 7 to 12 total days of treatment is typical, longer durations of treatment may be required.15

In the step down protocol, high initial doses of gonadotropins are used, and then halved during follicular recruitment and growth, aiming to mimic physiologic changes of endogenous FSH.36 To reduce multiple pregnancy, careful follow-up of follicular development by ultrasound is required. In patients with >2 follicles ≥16mm or ≥ 3 intermediate-sized follicles, cycle cancellation should be considered. In multifollicular development, conversion to in vitro fertilization (IVF) may also be an option.20 Once a mature follicle has developed, exogenous hCG is administered to stimulate ovulation followed by timed intercourse or intrauterine insemination. Currently, there are insufficient data on women with PCOS to recommend luteal support with progesterone.15

When it comes to combined therapy with metformin, Bordewijk et al found a higher cumulative live birth rate when compared with FSH alone, and insufficient evidence on multiple pregnancy rates and other adverse events.37 Palomba et al demonstrated that metformin administration significantly increases the live birth and pregnancy rates, and reduces the cancellation rate.38 International guidelines suggest the addition of metformin to gonadotropin stimulation to improve ovulation, pregnancy and live birth rates (evidence-based conditional recommendation, moderate quality of evidence).10

### Metformin

Metformin is an insulin sensitizer, from the biguanides class, commonly used as a first-line antihyperglycaemic treatment for type 2 diabetes. Metformin increases glucose uptake in the periphery, enhances insulin sensitivity in the liver and peripheral tissues and inhibits hepatic gluconeogenesis, hence lowering blood glucose levels without causing hypoglycaemia.39 Directly in the ovary, metformin lowers androgen production by theca cells, decreasing the activity of ovarian cytochrome P450c17a and expression of steroidogenic acute regulatory protein.40,41 Ovarian hyperandrogenism is responsible for premature follicular atresia and anovulation so metformin can theoretically have an ovulation stimulatory effect.42

Morley et al, in a recent Cochrane review, found that metformin alone compared with placebo may have higher rates of ovulation, clinical pregnancy and live birth, but superiority to CC alone was inconclusive.12 New international guidelines suggest that metformin can be used alone in women with PCOS, but patients should be informed that there are more effective ovulation induction agents.10

There is more supportive evidence for metformin use in combination with CC or gonadotropins and as adjunct in IVF vs intracytoplasmic sperm injection (ICSI) therapy, addressed in the respective sections of this review.

Doses used, alone or in combination, usually range from 1500 mg to 1700mg/d, divided into 2 to 3 doses, for non-fertility studies.10

Metformin may cause mild, self-limiting, gastrointestinal adverse effects that can be minimized by starting with a low dose of 500 mg and increasing weekly to a maximum dose of 1500mg.20 Abdominal discomfort, diarrhea, nausea, and vomiting, associated with modest weight loss, are the most commonly encountered symptoms.43

### Assisted reproductive technologies (ART)

ART, mainly IVF, ICSI and in vitro maturation (IVM), have a role in PCOS after failure to respond to pharmacological ovulation induction or if there are other indications such as tubal damage or male factor infertility.10 Given the lack of evidence, in PCOS patients, no ART is favored in current international guidelines.10

### In vitro fertilisation ± intracytoplasmic sperm injection

IVF, with or without ICSI, is recommended as a third-line treatment or in the presence of other infertility factors (clinical consensus conditional recommendation).10 Heijn et al meta-analysis found a similar chance for pregnancy or live birth per started IVF cycle between woman with PCOS and non-PCOS.44

Women with PCOS, who require IVF±ICSI, have significantly increased risk of developing OHSS due to excessive response to FSH stimulation.10 A GnRH antagonist protocol should be preferred over an agonist protocol, as a simple safer alternative to reduce the duration of stimulation, total gonadotropin dose and incidence of OHSS.10,45

GnRH agonist versus hCG for oocyte triggering proved effective in reducing OHSS.46 As this negatively impacts pregnancy outcomes in autologous cycles it can be followed by a “freeze-all” program (ie, embryo transfer is not performed in the fresh autologous cycle).46,47 Frozen embryo transfer is performed in a later cycle. The freeze-all strategy is beneficial for pregnancy outcomes in high responders with 15 or more oocytes retrieved.47
The initial phase of IVF ± ICSI comprises ovarian hyperstimulation to enable the recruitment of multiple follicles. For this purpose, the protocol usually includes the co-administration of GnRH-analogues and gonadotropins. In women with PCOS, who undergo IVF ± ICSI, there seems to be no difference between the use of urinary or recombinant follicle stimulating hormone, and no benefit in adding exogenous LH supplement. According to Cochrane Database of Systematic Review, clinicians should consider metformin treatment before and during an ART cycle for women with PCOS to reduce OHSS rates in ART cycles (evidence-based conditional recommendation, low quality of evidence).\(^{10,49}\)

**In vitro maturation.** IVM comprises the retrieval of immature oocytes from antral follicles, followed by in vitro final stages of meiosis maturation, under proper culture media additives.\(^{50}\)

Since no exogenous human gonadotropin stimulation is needed for the IVM technique, the risk of OHSS is considerably lower, even excluded, in comparison to the standard IVF technique.\(^{51,52}\) This is a key benefit, as PCOS patients have higher risk of OHSS due to their elevated antral follicle counts.\(^{51}\) Also, children conceived after IVM are not adversely affected.\(^{53}\)

Success rates, for live birth, following IVM, remain lower than traditional IVF but seem to have improved in recent years.\(^{51,52}\) A recent Cochrane review found no good quality evidence to support the recommendation of IVM in preference to IVF/ICSI.\(^{54}\)

Likewise, international guidelines, given the lack of evidence, do not favor IVM to other options.\(^{10}\)

**Laparoscopic ovarian drilling**

For women with anovulatory infertility who are resistant to pharmacological treatment, a minimally invasive surgical approach, laparoscopic ovarian drilling (LOD), may be an option for ovulation induction (evidence-based conditional recommendation, low quality of evidence).\(^{10,55}\)

The most successfully used technique is performing 5 to 10 perforations on the surface of the ovary, bilaterally, using monopolar energy.\(^{56}\)

The most suggested mechanism by which LOD leads to restoration of ovulatory function is that the destruction of androgen producing tissue, represented in the ovary by theca cells, leads to a decline in ovarian androgen production, reduction of peripheral androgen levels, with subsequent less conversion to estrogens.\(^{57,58}\)

As a result, a reduced negative feedback from estrogens on the hypothalamus leads to a fall in LH levels and an increase in FSH levels, appropriately reestablishing follicles’ stimulation.\(^{57,58}\)

Also, inside the ovary, the environment becomes predominantly estrogenic, which promotes follicular maturation and later ovulation.\(^{57,58}\)

The surgical approach has some advantages, in comparison to medical therapy, such as reduced risk of OHSS and multiple pregnancy, lower cycle cancellation rates in patients later submitted to IVF, and subsequently fewer direct and indirect costs.\(^{57,59}\)

On the other hand, a Cochrane review by Farquhar et al, found no significant difference between LOD and medical therapy on live birth pregnancy, miscarriage or OHSS rates.\(^{58}\)

Also, there is concern that this technique may cause diminished ovarian reserve and periadnexal adhesion formation. An unilateral drilling is generally advised, since there is “no evidence of a significant difference in rates of live birth, pregnancy, ovulation or miscarriage” when comparing to bilateral drilling.\(^{58,60}\)

Patients who are overweight or obese have higher risk of poor outcome and are more likely to develop complications.\(^{10,61}\)

Abu Hashim et al found other possible predictors of poor outcome such as long term infertility, marked hyperandrogenism, high levels of AMH and low levels of LH.\(^{61}\)

**Bariatric surgery**

Bariatric surgery is the most effective way for weight loss.\(^{62}\)

It attenuates PCOS’s associated clinical symptomatology, such as menstrual irregularity, hirsutism, and, possibly, infertility.\(^{20,63}\)

In patients trying to conceive after bariatric surgery, one meta-analysis reported up to 58% spontaneous conception rates.\(^{64}\)

It also can improve comorbidities as type 2 diabetes mellitus, hypertension, and dyslipidemia, and lower the risk of pre-eclampsia, gestational diabetes and large-for-gestational-age offspring in the bariatric population.\(^{10,20,63,65}\)

On the other hand, bariatric surgery has a potential risk for nutritional deficiencies, in the context of malabsorptive states.\(^{20,27}\)

This procedure has also been associated with shorter gestations, increased risk of small-for-gestational-age offspring and an increase in perinatal mortality.\(^{20,27,66}\)

The international guidelines suggest that, for the purpose of improving fertility and pregnancy outcomes, bariatric surgery should be considered an experimental therapy in women with PCOS (clinical consensus conditional recommendation against the option).\(^{10}\)

Balen et al proposes that bariatric surgery could be considered in women with PCOS, who have a BMI ≥ 35 kg/m², and who remain infertile despite conservative treatment for a minimum of 6 months (based on low quality evidence).\(^{21}\)

**Inositol**

Inositol (hexahydroxy cyclohexane) is a 6-carbon ring chemical compound, having a hydroxyl group linked to each carbon of the ring, with 9 possible stereoisomeric forms.\(^{67}\) Two of these are myo-inositol (MI) and D-chiro-inositol (DCI), which play different relevant biological functions as insulin-sensitizing agents.\(^{20}\)

In the ovary, MI mediates glucose uptake and FSH signaling, whereas DCI ameliorates insulin-induced androgen synthesis.\(^{20,68}\)

In PCOS patients, an imbalance in tissue availability of these compounds appears to contribute to IR.\(^{69}\)

A MI depletion and a DCI overload in the ovary, due to enhanced epimerase activity, also seems to impair oocyte quality.\(^{69}\)

There is some emerging data suggesting that PCOS patients’ supplementation with inositol has benefits on ovulation rate and metabolic and hormonal profiles.\(^{70}\)

Pundir et al found a significant improvement in ovulation rate and regularized menstrual cycles using inositol, compared with placebo.\(^{1}\)

Ozay et al found that MI administration increases clinical pregnancy rates, lowers total FSH dose and ovulation induction duration.\(^{2}\)

However, 2 recent Cochrane reviews, by Showell et al and Morley et al, found no good quality evidence to support the use of MI to improve live birth rate and clinical pregnancy rate, and to decrease miscarriage rate or multiple pregnancy rate, for subfertile women with PCOS undergoing IVF or ovulation induction.\(^{32,73}\)

Currently, given the lack of evidence, international guidelines recommend that inositol should be considered an experimental therapy in PCOS (evidence-based conditional recommendation against the option, very low quality of evidence).\(^{10}\)

**Vitamin D**

The prevalence of vitamin D insufficiency or deficiency in reproductive age women is 45% to 90%.\(^{74,75}\)

PCOS and vitamin D deficiency are both associated with IR.\(^{76}\)

A study found that vitamin D deficiency in women with PCOS...
who underwent ovarian stimulation for the treatment of infertility was associated with significantly diminished rates of ovulation, of pregnancy, and ultimately a reduced chance of live birth.\(^7^7\)

Vitamin D supplementation may be recommended as a potential therapeutic adjunct for the ovulatory dysfunction and metabolic disorders observed in women with PCOS. Controlled prospective randomized trials are needed to reach definitive conclusions regarding the role of supplementation with vitamin D in female reproduction.

**Alternative therapies**

Currently, the use of acupuncture for infertility treatment in women with PCOS is not supported by the very low quality evidence available.\(^7^8\)–\(^8^0\) In regards to Chinese Herbal Medicine, there is also preliminary very low quality evidence on the enhancement of fertility outcomes.\(^8^1\)–\(^8^3\)

**Conclusion**

PCOS is a complex reproductive, metabolic, and psychological disorder characterized by a variety of clinical manifestations and a major cause of infertility.

Lifestyle changes should be considered first-line treatment recommendation for PCOS related infertility, before resorting to pharmacological options. Ovulation induction is the next step, being letrozole the first choice, followed by CC. In women who have failed first line oral ovulation induction therapy, gonadotropins are the next line. For women who do not become pregnant with ovulation induction drugs or have additional infertility factors, ART or LOD can be used (Fig. 3).

In patients with IR or hyperinsulinemia, metformin use in combination with CC or gonadotropins and as adjunct in IVF±ICSI therapy is still the best regimen recommended (Fig. 3).

Bariatric surgery can improve comorbidities associated with PCOS, but, at this time, should be considered experimental as a fertility therapy. Insulinol and vitamin D may be useful, but further research is needed to be recommended.

Alternative therapies have no clear evidence for efficacy.

**Conflicts of interest**

Authors have declared no conflict of interest.

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