



Polycystic Ovary Syndrome: Fertility Treatment Options

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10.1 Introduction

Polycystic ovary syndrome (PCOS) is one of the most prevalent causes of infertility, as it comprises the most common endocrine disorder in premenopausal women. The main pathophysiological mechanism, anovulation, results in an increased time-to-conception.

During the second international symposium, held in Thessaloniki in 2007, and adopted by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), all the therapeutic options regarding fertility for women with PCOS were discussed [1]. Recently, the International Evidence-Based Guideline for the Assessment and Management of PCOS addressed all fertility treatment options and critically appraised the available evidence [2].

10.2 Fertility Treatment Options

10.2.1 Lifestyle Change for Weight Loss

Lifestyle interventions include diet, physical exercise and behavioral management techniques. Lifestyle changes to induce weight loss are considered the first-line treatment for infertility in women with PCOS, with parallel overall health, metabolic, and psychological benefits. It has been suggested that lifestyle modifications should be advised and implemented in obese women with PCOS before the ovulation induction, mainly to avoid obesity-related pregnancy complications;

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nevertheless, it is unclear if this approach increases the cumulative pregnancy or live birth rates. A recent Cochrane review on lifestyle changes in women with PCOS, which synthesized 15 studies with 498 participants, showed that lifestyle interventions could have a positive impact on the free androgen index (FAI) [mean difference (MD) -1.11, 95% confidence interval (CI) -1.96 to -0.26, 6 randomized controlled trials (RCTs), $n = 204$, $I^2 71\%$]. Unfortunately, no studies were found reporting data on miscarriage, pregnancy or live birth rates [3]. In any case, obesity constitutes an independent risk factor for anovulation, failed or delayed response to treatment [e.g., clomiphene citrate (CC), gonadotropins], first trimester miscarriages, and third trimester complications. Thus, weight loss is recommended as a first-line treatment for obese women with PCOS desiring fertility. No type of diet seems to be more beneficial compared with the others [4]. A moderate reduction in body weight (5–10%) in overweight women can restore menstruation and fertility.

10.2.2 Pharmacological and Surgical Ovulation Induction

Letrozole and CC are the treatment of choice for ovulation induction in women with PCOS. CC has traditionally been used as an ovulation induction agent for over 40 years. Nevertheless, according to recent data, letrozole is more effective compared with CC in anovulatory women with PCOS, with the likelihood of a live birth increasing by 40–60% with letrozole compared to CC [5].

10.2.2.1 Letrozole

Letrozole is the most common aromatase inhibitor (AI) used for ovulation induction. AIs inhibit the aromatase action, the enzyme that converts androgens to estrogens and increase the secretion of follicle-stimulating hormone (FSH) needed to stimulate the development and maturation of the ovarian follicle. A 2019 individual patient data (IPD) meta-analysis assessing letrozole vs. CC showed that letrozole leads to higher ovulation [relative risk (RR) 1.13, 95% CI 1.07–1.2], clinical pregnancy (RR 1.45, 95% CI 1.23–1.70, I^2), and live birth rates (RR 1.43, 95% CI 1.17–1.75) compared with CC [6]. Similarly, letrozole decreased the time-to-pregnancy [(hazard ratio [HR] 1.72, 95% CI 1.38–2.15)] [6]. These observations are more evident in women with high baseline serum concentrations of total testosterone. According to the 2018 International Evidence-Based Guideline for the Assessment and Management of PCOS, letrozole comprises a first-line pharmacological treatment for ovulation induction in women with PCOS [2]. Despite this evidence as well as its affordable cost, the use of letrozole remains off-label, and women have to provide informed consent.

10.2.2.2 Clomiphene Citrate

CC is a selective estrogen-receptor modulator (SERM) traditionally used as an ovulation induction agent for over 40 years. Compared with placebo or no treatment, CC leads to higher clinical pregnancy rates. Its primary indication is infertility due to oligoovulation or anovulation. CC is administered at a starting dose of 50 mg/day and is taken orally for 5 days. It is a cheap and safe drug, as it does not require

frequent ultrasound monitoring. It is taken orally and has relatively few adverse effects. Multiple pregnancy rates with CC administration range from 0.3% (triplets) to 5–7% (twin pregnancies), and the risk for developing ovarian hyperstimulation syndrome (OHSS) is <1% [7].

10.2.2.3 Metformin

Metformin is a simple, low-cost, and safe treatment option for obese women with PCOS. Metformin is an insulin-sensitizing drug, taken orally twice daily. Although it is commonly associated with gastrointestinal disorders, there are no other serious adverse effects. A recent Cochrane meta-analysis, which included 41 studies and 4552 women, showed that metformin increases ovulation [odds ratio (OR) 2.64, 95% CI 1. –3.75; I^2 61%; 13 studies, 684 women), clinical pregnancy (OR 1.98, 95% CI 1.47–2.65; I^2 30%; 11 studies, 1213 women), and live birth rates (OR 1.59, 95% CI 1.00–2.51; 4 studies, 435 women) compared to placebo [8].

In obese women with PCOS, CC could be used in combination with metformin to improve the reproductive outcomes (ovulation, pregnancy, and live birth rates) [2]. The addition of metformin to CC may also decrease the time-to-pregnancy, especially in specific PCOS subgroups (e.g., obese and CC-resistant women). When metformin and CC are compared; in terms of their efficacy on the reproductive outcomes, the baseline body mass index (BMI) seems to play a role: normal-weight women benefit more from metformin. In contrast, obese women with PCOS have better reproductive outcomes (clinical pregnancy and live birth rates) after ovulation induction with CC [8].

10.2.2.4 Gonadotropins

Gonadotropins are used as a second-line treatment for ovulation induction in women with PCOS. This strategy is mainly due to their cost, availability, as well as the need for expertise and intensive ultrasound monitoring. In addition, the risk of multiple pregnancies is increased. The clinical efficacy of the different gonadotrophin preparations seems comparable. As women with PCOS receiving exogenous gonadotropins are at an increased risk for developing OHSS, a low-dose, step-up ovarian stimulation protocol has been suggested.

10.2.2.5 Assisted Reproduction Technology

About one-fifth of women undergoing assisted reproduction technology (ART) have been diagnosed with PCOS. However, in vitro fertilization (IVF) should only be used in the event of failure of other treatments in women with PCOS, due to the lack of consistency in stimulating the ovaries in a controlled manner, or if there are specific indications for IVF, e.g., tubal or male factor infertility. Although there is no agreement on the optimal stimulation protocol, most studies indicate that the use of GnRH-antagonists per se can significantly reduce the risk of developing OHSS compared to other protocols [9]. Moreover, in an antagonist protocol, it is possible to induce final oocyte maturation with GnRH-agonist triggering instead of hCG, which, associated with freezing of all embryos and subsequent frozen embryo transfer (FET), maintains high pregnancy rates and almost eliminates the risk for OHSS [10]. Additionally, IVF is a reasonable treatment strategy, since multiple pregnancy

rate can be minimized by single embryo transfer (SET), which is not the case with ovulation induction and especially gonadotrophin administration. It is important to note that with IVF, women with PCOS have similar pregnancy rates compared with women without PCOS.

10.2.2.6 Ovarian Drilling

There is insufficient evidence that laparoscopic ovarian diathermy (“drilling”) in CC-resistant women is associated with increased rates of clinical pregnancies and live births compared with other treatments [5]. However, a reduction in the incidence of multiple pregnancies has been observed in women undergoing laparoscopic ovarian drilling [11]. The main concerns for its use are related to the long-term effects on the ovarian function and the development of intra-abdominal adhesions.

10.2.3 Other Treatment Options to Enhance Fertility

Alternative assisted reproduction options in women with PCOS include in vitro maturation (IVM) of eggs collected from unstimulated ovaries [12]; as the method requires considerable expertise, it is not available widely. Given the current evidence, the use of anti-obesity medications aiming at improving fertility is not justified [5].

According to an overview of systematic reviews of non-pharmacological interventions in women with PCOS, N-acetyl-cysteine and inositol could induce ovulation, though the evidence is not strong [13]. Regarding alternative medicine, Chinese herbals and acupuncture on top of pharmacological therapies for ovulation induction in women with PCOS may improve clinical pregnancy rates compared with pharmacological therapies alone [13].

10.3 Selecting the Optimal Fertility Treatment Option

A meta-analysis of 57 RCTs, which studied 8082 women who were treated with CC, metformin (or their combination), tamoxifen, FSH, or laparoscopic ovarian drilling, demonstrated that all pharmacological treatments result in a higher pregnancy rate compared with placebo or no treatment [14]. Letrozole and the combination of CC with metformin resulted in higher pregnancy rates compared to CC, tamoxifen, or metformin alone [14]. An IPD meta-analysis demonstrated that letrozole improved time-to-pregnancy (HR 1.72, 95% CI 1.38–2.15), clinical pregnancy rates (RR 1.45, 95% CI 1.23–1.70), and live birth rates (RR 1.43, 95% CI 1.17–1.75) compared with CC [6].

10.4 Conclusions

Women with PCOS and infertility should be reassured that many treatment options are available. A moderate reduction in body weight (5–10%) in overweight women can restore fertility, without taking any other measure. First-line treatments include

lifestyle modifications and CC/letrozole, while second-line treatments include medications that increase insulin sensitivity, exogenous gonadotropins, and laparoscopic ovarian drilling. The choice of treatment should be the result of a joint decision after an informed discussion between the infertile couple and the medical team, based on a woman's special characteristics and the couple's wishes and choices.

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