

# Fertility Treatment Options for Women With Polycystic Ovary Syndrome

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**ABSTRACT:** Polycystic ovary syndrome is the most common endocrinological disorder in women of reproductive age. It is commonly associated with anovulatory subfertility, for which there are a range of treatment options available to help them conceive. These options are given in a step-wise manner with an appropriate selection of patients to maximise success rates with minimal complications. This review discusses the importance and involvement of multidisciplinary care when offering treatment to women with subfertility. Multidisciplinary care gives an excellent opportunity to identify, assess risk, and potentially prevent future morbidities and complications while treating women for fertility issues. We have also summarised the various options available for fertility treatment: pharmacological treatments, nonpharmacological intervention, and assisted reproductive technology.

**KEYWORDS:** PCOS, fertility, ovulation induction, IVF

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## Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrinological disorders in women of reproductive age, affecting 5% to 10% of these women.<sup>1</sup> Anovulatory infertility is a common consequence of PCOS, and the incidence of PCOS in women with anovulatory infertility is higher at 70% to 80%.<sup>2</sup> Hence, the fertility treatment options offered to these women are predominantly centred on treating anovulation. However, women with PCOS often have other comorbidities such as an increased body mass index, cardiometabolic syndrome, mental health disorders and a lower health-related quality of life (HQoL).<sup>3</sup> A multidisciplinary approach incorporating preconception risk assessment and optimisation of health, improved HQoL, and lifestyle interventions is recommended prior to commencing pharmacological treatment with the aim of improving fertility and other reproductive outcomes. These evaluations and treatments are initiated in primary care with referrals to other relevant specialities when needed.

In this article, we aim to summarise the options for fertility treatment in women with PCOS. These include nonpharmacological interventions, pharmacological interventions, and assisted reproduction treatments. Treatments for other aspects of the condition are outside the scope of this review and may be dealt with in other sections of the issue.

## Nonpharmacological Interventions

About 40% to 60% of women with PCOS are overweight or obese.<sup>4</sup> Obesity is known to perpetuate PCOS as abdominal adiposity results in increased insulin resistance leading to increased ovarian hyperandrogenism<sup>5</sup> causing the symptoms of PCOS such as hirsutism, anovulation, and infertility. Increased insulin resistance also leads to subsequent impaired glucose tolerance and other metabolic abnormalities like diabetes mellitus, metabolic syndrome, and an increased risk for cardiovascular disease. Hence, it is imperative to address and treat obesity.<sup>4</sup>

Weight loss has demonstrated improvements in endocrine function like reduction in testosterone and free androgen index (FAI), increased sex-hormone-binding globulin, and improvements in metabolic profiles like lipids and total cholesterol. Seven studies from a systematic review<sup>6</sup> compared the effect of weight loss on hormonal profiles in PCOS and non-PCOS women. They reported an improvement in hormonal values in non-PCOS women greater than PCOS women. However, there was a drop in total testosterone and FAI that was observed in PCOS women.

A study by Panidis et al<sup>7</sup> showed a statistically significant decrease ( $P < .001$ ) in serum total testosterone and FAI with weight loss. The prevalence of metabolic syndrome is 33% in women with PCOS.<sup>8,9</sup> Weight loss helps to improve not only metabolic syndrome but also psychological affection which shows a 3- to 8-fold increased prevalence in women with PCOS.<sup>10</sup> Weight loss may be achieved through lifestyle modifications like diet, exercise, and behavioural therapy.

## Life Style Modification

### Exercise

Exercise and dietary regulation are important components of lifestyle modification. These have demonstrated substantial improvement in cardiovascular risk factors and reproductive dysfunction, essentially anovulation in women with PCOS.<sup>11</sup>

A systematic review was conducted by Harrison et al<sup>12</sup> to identify the effect of exercise on clinical outcomes in PCOS. Five out of 8 studies in this review reported on reproductive outcomes after lifestyle intervention, in which a total of 256 participants were pooled and 141 received the exercise intervention. Three studies reported a significant improvement in menstrual regularity and ovulation. Thomson et al<sup>13</sup> reported results for menstrual function in 59 out of a total of 94 participants following a 20-week exercise intervention. About 49% of



these reported an overall improvement in ovulation and menstrual cyclicity.<sup>13</sup>

Most of these studies involved moderate intensity physical activity and demonstrated a consistent improvement in ovulation, reduced insulin resistance (9%-30%) and weight loss (4.5%-10%).<sup>12</sup>

Another review by Moran et al,<sup>14</sup> with 164 participants in 6 studies compared different lifestyle interventions like physical exercise, dietary modifications, and behavioural therapy, demonstrated a significant decrease in testosterone, reduced body weight, abdominal fat, body hair growth, and insulin resistance. Total testosterone showed a mean difference (MD) of  $-0.27$  nmol/L, (95% confidence interval [CI]:  $-0.46$  to  $-0.09$ ,  $P=.004$ ) hirsutism or excess hair growth by the Ferriman-Gallwey score which showed an MD of  $-1.19$ , (95% CI:  $-2.35$  to  $-0.03$ ,  $P=.04$ ), weight loss showed an MD of  $-3.47$  kg, (95% CI:  $-4.94$  to  $-2.00$ ,  $P<.00001$ ), waist circumference showed an MD of  $-1.95$  cm (95% CI:  $-3.34$  to  $-0.57$ ,  $P=.006$ ), and fasting insulin showed an MD of  $-2.02$   $\mu$ U/mL (95% CI:  $-3.28$  to  $-0.77$ ,  $P=.002$ ).

Due to heterogeneity of various study designs, the optimal duration and type of exercise is difficult to establish. Regular exercise of 150 min/week including at least 90 minutes moderate intensity aerobic activity is recommended to improve cardiometabolic outcomes by Teede et al.<sup>15</sup>

The new international PCOS guideline recommends a minimum of 150 min/week of moderate intensity physical activity or 75 min/week vigorous intensity and muscle strengthening activities on 2 nonconsecutive days/week. For modest weight loss, a minimum of 250 min/week of moderate intensity activities or 150 min/week of vigorous intensity is recommended.<sup>3</sup>

The muscle strengthening activities involving major muscle groups to be done on 2 nonconsecutive days/week.<sup>3</sup>

### Diet

A low-calorie diet with adequate nutritional intake and healthy food choices have improved fertility outcome in PCOS by significantly improving insulin sensitivity. A randomised controlled trial (RCT) by Mehrabani et al<sup>16</sup> and a systematic review by Moran et al,<sup>17</sup> on dietary composition in treatment of PCOS found improved menstrual regularity, greater reduction in insulin resistance, total and high-density lipoproteins with low carbohydrate and low glycaemic index diets and improved depression and self-esteem was observed in a high-protein diet. A reduction in insulin resistance also reduces risks such as type 2 diabetes, dyslipidemia, and heart disease in the long term.<sup>18</sup> Existing evidence supports the benefits of healthy diet. Essentially a diet moderate in carbohydrates, high in fibre, and moderate with respect to polyunsaturated and monounsaturated fats, with more percentage of lean sources of protein is recommended<sup>18</sup> and to have the maximum benefits, it is important to adopt healthy eating patterns which is to take small portions in frequent intervals.<sup>15</sup> The current recommendations

to achieve weight loss in those with excess weight, aims at achieving an energy deficit of 30% or 500 to 750 kcal/day (1200-1500 kcal/day) and the ways to achieve above the diet should be formulated and planned.<sup>3</sup>

### Behavioural Therapy

Increased body mass index (BMI) or other clinical features of PCOS like hirsutism can severely affect body image. Body image distress is associated with depression.<sup>19,20</sup> Depression can impact the motivation required for efforts at self-care negatively and can further evolve due to several repeated unpleasant experiences or failed attempts in improving lifestyle.<sup>21</sup>

Adequate treatment of depression improves PCOS symptoms of self-perception and quality of life (QOL) dysfunction.<sup>21</sup> In addition, treatment of distressing PCOS clinical symptomatology may improve depression features. Pharmacotherapy and psychotherapy are both effective treatment modalities for depression symptoms, and evidence supports a combined approach as most effective. Hence, identifying women with body image distress and depression is very important, and offering targeted therapies like cognitive behavioural therapy should be considered to ameliorate depression and improve QOL.<sup>22</sup>

A variety of cross-sectional studies support the positive outcomes of exercise for the mental health of women with PCOS. Liao et al<sup>23</sup> have demonstrated that a 6-month programme of brisk walking can reduce significantly body image distress, despite no change in BMI in these patients. In this study, 35 women with  $BMI \geq 25$  kg/m<sup>2</sup> participated. Twenty-three returned 6 months later for reassessment. Of these, 12 completed the exercise programme. Preassessment and postassessment showed a significant reduction in body image distress for the completers ( $P<.01$ ) in spite of no significant change in BMI.<sup>23</sup> As the number of participants was low, the recommendations were put forward for a RCT.

Silveira et al<sup>24</sup> have demonstrated that exercise may contribute to improved psychological functioning directly. A meta-analysis was conducted to evaluate the effect of aerobic and strength training as a treatment for depression. Ten articles were selected. The effect of strength and aerobic exercise effect was combined, which showed a standard mean deviation of 0.61 (95% CI: 0.88-0.33), reduction in depression symptoms in intervention group than nonintervention group. ( $P<.001$ ). Due to the heterogeneity in the studies, the pooled effect size by standardised mean differences (SMDs) was used. Individually, there was a reduction of 0.52 (95% CI:  $-0.79$  to  $-0.25$ ) and 0.96 (95% CI:  $-1.97$  to 0.05) in standard deviations for aerobic activity and strength training, respectively. A statistically significant difference between aerobic training and control group ( $P=.001$ ) and a trend towards significance when strength training and control groups were compared ( $P=.52$ ).<sup>24</sup>

### Pharmacological Treatment

The principle of pharmacological fertility treatment in women with PCOS is to treat anovulation as PCOS represents 80% of

anovulatory World Health Organization (WHO) type II infertility.<sup>25</sup>

### Oral Agents

Oral ovulation induction agents, such as clomiphene citrate (CC) and letrozole, and an insulin sensitiser, such as metformin, are the first-line pharmacological treatment for anovulatory infertility and no other infertility factors in women with PCOS.

### Clomiphene Citrate

Clomiphene citrate, a nonsteroidal triphenylethylene derivative, has been used as the first-line treatment for ovulation induction treatment for several years. It is a mixture of 2 geometric isomers, enclomiphene and zuclomiphene in a ratio of 3:2. Enclomiphene is more potent and has a very short half-life.<sup>26</sup> Clomiphene citrate is a selective oestrogen receptor modulator (SERM) acting on the hypothalamic pituitary axis, inhibiting oestrogen receptors and hence the negative feedback of oestrogen on the release of pituitary gonadotropins. This stimulates an increased pituitary gonadotropin release that, in turn, drives ovarian follicular activity.<sup>27</sup> In anovulatory women with PCOS in whom the GnRH pulse frequency is already abnormally high, CC treatment increases pulse amplitude but not frequency.<sup>26,28</sup> During CC treatment, levels of both luteinising hormone (LH) and follicle-stimulating hormone (FSH) increase after the typical 5-day course of therapy.<sup>29</sup>

Clomiphene citrate is administered orally, typically for 5 days starting on the second day after the onset of spontaneous or progestin-induced menstrual cycle.<sup>30</sup> Treatment begins with starting dose, single 50-mg tablet daily for 5 consecutive days, stepping up by 50-mg increments in subsequent cycles until ovulation is induced or a maximum dose of 150 mg is reached. A course of 3 to 6 cycles is recommended. About 75% to 80% women with PCOS will ovulate after CC, and a conception rate of 22% per cycle has been reported.<sup>30</sup> This discrepancy between ovulation and pregnancy rates is thought to be related to the antioestrogenic effect of CC on endometrial receptivity and cervical function.<sup>31</sup> In addition, increased LH secretion due to CC may reduce the chances of pregnancy.<sup>32</sup> Clomiphene citrate is a safe drug with minimal side effects. However, due to the possibility for multifollicular growth and antioestrogenic endometrial effects, careful monitoring of ovarian response and endometrial thickness with serial ultrasound scans is imperative. Twin pregnancy and triplets with CC are 5% to 7% and 1.1%, respectively.

### Letrozole

Although letrozole was originally used for clomiphene resistance and failure, it is currently considered as a first-line agent for ovulation induction.<sup>3</sup> It is an aromatase inhibitor which blocks the conversion of androgens to oestrogens in the ovarian follicles, peripheral tissues, and in the brain. This results in a decrease in circulating and local oestrogens with an increase in

intraovarian androgens. A decrease in oestrogen levels releases the hypothalamo-pituitary-ovarian (HPO) axis from the negative feedback of oestrogens, resulting in a surge in FSH release which drives follicular growth. Since, the HPO axis feedback mechanism is intact, normal follicular growth, selection of dominant follicle, and atresia of smaller growing follicle occurs, thereby facilitating monofollicular growth and ovulation. Increasing the intraovarian androgens increases the follicular sensitivity to FSH. Recent data show the role of androgens in early follicular developments by augmenting FSH receptors and stimulating insulin-like growth factor (IGF)-I. Follicle-stimulating hormone and IGF-I act synergistically to promote follicular growth. Letrozole is administered at 2.5 to 7.5 mg daily for 5 days.<sup>33</sup>

Many systematic reviews and RCTs with moderate- to high-quality evidence demonstrate letrozole to be a superior drug than clomiphene for clinical pregnancy rate and live birth rate. In addition, there is high-quality evidence to demonstrate reduced ovarian hyperstimulation syndrome (OHSS) rates when letrozole is used for ovulation induction (OI) rather than clomiphene.

A systematic review including 7 RCTs compared CC with letrozole in women with PCOS. The meta-analysis demonstrated a significantly higher pregnancy rate and live birth rate per patient for letrozole as compared to CC.<sup>34</sup> Overall, these studies accounted for 1833 patients (906 in the letrozole group and 927 in the CC group) and for 4999 ovulation induction cycles (2455 in the letrozole group and 2544 in the CC group). Five of the included studies reported data on live birth rate. There was a statistically significant increase in the live birth and pregnancy rates in the letrozole group when compared to the CC group (Risk ratio, RR=1.55, 95% CI: 1.26-1.90 and RR=1.38, 95% CI: 1.05-1.83) for live birth and pregnancy rates, respectively.

There were no differences in the multiple pregnancy, miscarriage, and ovulation rates between the 2 groups. This study demonstrated that letrozole is superior to CC when considering the live birth and pregnancy rates in patients with PCOS.<sup>34</sup>

Another large multicentre double-blind RCT by Legro et al<sup>35</sup> with 750 women showed that letrozole improved pregnancy outcome compared with CC. There was a higher cumulative ovulation rate with letrozole, 61.7% versus 48.3% with CC ( $P < .001$ , odds ratio [OR]: 1.16, 95% CI: 1.08-1.24).<sup>35</sup> In addition, live birth rates were achieved in 27.5% in the letrozole group compared to 19.1% in the clomiphene group. (OR: 1.44, 95% CI: 1.10-1.87.). There were no significant differences in the pregnancy loss (31.8% in letrozole group and 29.1% in the CC group) or twin pregnancy (3.4% and 7.4%).<sup>35</sup>

A 2014 Cochrane review, of 26 RCTs (5560 participants) reported the clinical pregnancy rate with letrozole to be higher than CC (OR: 1.40, 95% CI: 1.18-1.65).<sup>36</sup>

In another recent Cochrane database review<sup>37</sup> with inclusion of 42 RCT, and participation of 7935 women, letrozole was compared with clomiphene and laparoscopic ovarian drilling.

The live birth rates were higher with letrozole compared to CC (OR: 1.68, 95% CI: 1.42-1.99; 2954 participants; 13 studies). There is high-quality evidence that OHSS rates are similar with letrozole or CC (0.5% in both arms: risk difference [RD]: -0.00, 95% CI: -0.01 to 0.00 with 2536 participants).<sup>37</sup> A moderate-quality evidence demonstrated a higher pregnancy rate in favour of letrozole (OR: 1.56, 95% CI: 1.37-1.78; 4629 participants; 25 studies). There is little or no difference between treatment groups in the rate of miscarriage by pregnancy (20% with CC versus 19% with letrozole) OR: 0.94, 95% CI: 0.70 to 1.26; 1210 participants and multiple pregnancy rate (1.7% with CC versus 1.3% with letrozole); OR: 0.69, 95% CI: 0.41 to 1.16; 3579 participants; 17 studies.<sup>37</sup>

A systematic review and network meta-analysis conducted by Wang et al, in which 8082 women were included in 57 trials, found that the clinical pregnancy rate of letrozole was significantly higher than clomiphene with an odds ratio of 1.58 (95% CI: 1.25-2.00). For the ovulation rates, the odds ratio was of 1.99 (95% CI: 1.38-2.87). Letrozole also led to higher live birth rates when compared with clomiphene alone (OR: 1.67, 95% CI: 1.11-2.49). It also was found to have lower rate of multiple pregnancy with odds ratio of mere 0.46 (95% CI: 0.23-0.92).<sup>38</sup> This systematic review also recommended letrozole as a first-line treatment due to its higher ovulation, pregnancy, and live birth rate and lower multiple pregnancy rate.<sup>38</sup>

Letrozole is a well-tolerated drug, and despite of promising results letrozole has shown in recent studies, it continues to remain off label in many countries. Concerns were raised about its teratogenic effects in an abstract and possible risk of congenital anomalies like locomotor malformation and cardiac anomalies, which was presented at American Society for Reproductive Medicine annual meeting in 2005. However, this risk remains below 5%.<sup>38,39</sup>

A distinct advantage of letrozole is that it does not have the antioestrogenic actions on the endometrium and cervical mucus. An intact HPO axis leads to monofollicular development, leading to reduced risks of multiple pregnancy.<sup>40</sup>

## Metformin

Metformin (1,1-dimethylbiguanide hydrochloride) is a biguanide currently used as an oral insulin-sensitising agent. Metformin inhibits hepatic glucose production, decreases intestinal glucose uptake, and increases insulin sensitivity in peripheral tissues.<sup>41</sup> Metformin plays its role in improving ovulation induction in women with PCOS through actions, such as reducing insulin levels and altering the effect of insulin on ovarian androgen biosynthesis, theca cell proliferation, and endometrial growth. In addition, potentially through a direct effect, it inhibits ovarian gluconeogenesis and thus reduces ovarian androgen production.<sup>42,43</sup>

Metformin is available as 500-, 850-, and 1000-mg tablets with an average dose of 1500 mg per day.<sup>39</sup> Metformin may be used as an adjunct to other ovulation induction agents or by itself in women PCOS with no other fertility factors.<sup>3</sup> Metformin has

shown to effect the metabolic and reproductive aspects of PCOS. A study by Kurzthaler et al<sup>44</sup> demonstrated the short-term effects of metformin compared to placebo on basal and LH-stimulated androgen secretion as well as on hormonal and metabolic parameters in 19 women with PCOS during a randomised, double-blinded placebo-controlled clinical trial. The study demonstrated that metformin was associated with a borderline significant reduction in the FAI ( $P=.05$ ) and with a reduction in the serum concentration of LH-stimulated testosterone (T) ( $P=.03$ ).<sup>44</sup>

Long-term studies have shown improvement in menstrual abnormalities in about 50% after use of metformin.<sup>45</sup> A recent update of the Cochrane review of insulin-sensitising agents and PCOS included 4227 participants. Treatment with metformin (3848 participants) showed improvement in clinical pregnancy rate compared to placebo (OR: 1.93, 95% CI: 1.42-2.64, 9 RCTs, 1027 women).<sup>46</sup> Live birth rate with metformin was also demonstrated to be higher than placebo in a Scandinavian study of 329 women comparing metformin and placebo (OR: 1.64; 95% CI: 1.02-2.63).<sup>47</sup>

A systematic review combining 5 studies and 741 women as participants metformin in comparison with clomiphene showed no conclusive evidence of a difference between the groups, with high heterogeneity OR: 0.71, 95% CI: 0.49 to 1.01. However, in the subgroup analysis by obesity status, there was evidence of a difference between the subgroups. Among obese women, live births were lower in the metformin group (OR: 0.30, 95% CI: 0.17-0.52, 2 studies, 500 women). In the nonobese subgroup, the direction of effect favoured metformin with high heterogeneity (OR: 1.71, 95% CI: 1.00-2.94, 3 studies, 241 women).<sup>46</sup>

Another systematic review comparing metformin with CC showed no difference in ovulation rate, pregnancy rate, and live birth rate between the two.<sup>46</sup>

However, when considering women with a BMI >30, CC was more effective than metformin for ovulation rate, pregnancy rate, and live birth rate.<sup>46</sup> The combination of metformin with clomiphene compared to clomiphene alone demonstrated a higher pregnancy rate with OR of 0.81 (95% CI: 1.35-2.42) and ovulation rates with OR of 1.55 (95% CI: 1.02-2.36).<sup>38</sup>

Pregnancies are more likely to be singleton with metformin and have a lower risk of OHSS.<sup>38</sup>

## Second-line Agents

### Gonadotrophins

The isolation of human gonadotropins, from pituitary gland and subsequently menopausal urine introduced a new era of treatment for anovulatory infertility in sixties.<sup>48,49</sup>

Refinement in gonadotropins production led to purification in urinary FSH resulting in purified and highly purified FSH and then recombinant FSH became common in use since 1996.<sup>50</sup> Follicle-stimulating hormone directly stimulates ovaries resulting in follicular development.

Gonadotropins are used as second-line agents for ovulation induction following unsuccessful treatment with first-line oral ovulation induction agents. This includes those women who are resistant to oral agents or have the undesirable antioestrogenic side effects on the endometrium. Ovulation induction in these women, especially those who are resistant to antioestrogens, is clinically challenging, as it is difficult to predict response to gonadotropin stimulation and achieve monofollicular development which is the desirable outcome. Hence, careful monitoring of the treatment cycles with ultrasound to prevent OHSS and a strict cycle cancellation policy when more than 2 follicles greater than 14 mm develop are put in place.<sup>51</sup>

A prospective multicentre RCT conducted by Homburg and Insler<sup>32</sup> demonstrated a significantly higher clinical pregnancy rate, live birth rate, time to pregnancy, and cumulative pregnancy rate over 3 treatment cycles in treatment-naïve patients with anovulatory PCOS for gonadotropins compared to clomiphene. Total women participated in this study were 302. They were randomised to OI with FSH, with 132 women and total 288 cycles and CC with 123 and total 310 cycles. They found per cycle outcome was superior after OI with FSH than with CC with respect to pregnancy rate per first cycle 30% versus 14.6%, respectively, with CI: 5.3 to 25.8,  $P = .003$ , pregnancy rate per woman, 58% versus 44% of women, 95% CI: 1.5 to 25.8,  $P = .03$ , live birth rate per woman was 52% versus 39%, 95% CI: 0.4 to 24.6,  $P = .04$ , cumulative pregnancy rate 52.1% versus 41.2%,  $P = .021$ , and cumulative live birth rate 47.4% versus 36.9%,  $P = .031$ , within 3 cycles of OI.<sup>32</sup>

The risk of multiple pregnancy was found to be significantly reduced by using a low-dose stimulation protocol. Another major problem with gonadotropin induction of ovulation has been the high incidence of OHSS<sup>50</sup> that too was significantly reduced using step-up low-dose regimen. Balen et al<sup>51</sup> discussed the use of a low-dose 'step-up' regimen or a step-down protocol to reduce the risk of multiple pregnancy or OHSS, where FSH was used for ovulation induction. Low-dose FSH regimen has been accepted and recommended by a few authors as a best practice in the case of clomiphene-resistant PCOS. In addition, there is now enough evidence to demonstrate its efficacy and relative safety in reducing the rates of multiple pregnancy and OHSS.<sup>51</sup>

A single-centre RCT<sup>52</sup> compared the efficacy of CC and low-dose recombinant FSH as first-line pharmacological therapy for anovulatory infertility. In this study 76 infertile women with PCOS were randomised for intervention (CC group,  $n = 38$ ) or recombinant human FSH (FSH group,  $n = 38$ ) in a chronic, low-dose, step-up protocol (daily starting dose = 75 IU) for 3 consecutive cycles. About 104 CC cycles and 91 FSH cycles were studied. The relative risk in FSH-induced cycles was 1.17 (95% CI:  $-0.97$  to  $-1.46$ ) for ovulation with human chorionic gonadotropin (HCG), 1.78 (0.92-3.54) and 1.83 (0.79-4.40) for the pregnancy rate, and live births per woman, respectively, in favour of FSH over clomiphene. The cumulative pregnancy rate after 3 treatment cycles was 43%

with FSH and 24% with CC ( $P = .06$ ).<sup>52</sup> This RCT suggests that low-dose recombinant FSH could be an effective alternative to CC in first-line treatment for anovulatory PCOS patients. However, another meta-analysis of the 2 studies for clinical pregnancy rate found that CC was better than gonadotropins OR 0.61 (0.40, 0.93),  $P = .021$ .<sup>39</sup> The new PCOS guideline published in 2018 recommends gonadotropins use in preference to clomiphene and metformin particularly in clomiphene-resistant cases. A systematic review by Abu Hashim et al<sup>53</sup> conducted meta-analysis in 263 women, demonstrated FSH is better for ovulation induction than clomiphene and metformin combined, OR: 0.13; 95% CI: 0.07-0.25;  $P < .00001$ . However, there was no statistically significant difference between the 2 interventions for multiple pregnancy rate OR: 0.33; 95% CI: 0.06-1.68;  $P = .18$ . In some cases, metformin could be added to gonadotropins to give better ovulation, pregnancy, and live birth rates.<sup>54</sup>

Various observational studies have been conducted to compare the outcome of various forms of FSH and their use in clomiphene-resistant or failed cycles. Weiss et al<sup>55</sup> in a meta-analysis of 14 trials in 2015 found no difference in clinical pregnancy, live birth rates, or OHSS among the various preparations of gonadotropins used. Ten trials compared recombinant follicle stimulating hormone (rFSH) with highly purified FSH, and 4 trials compared purified with highly purified FSH.

Gonadotropins may be considered as a first-line treatment in some circumstances, where availability and affordability is not a significant issue, accessibility to ultrasound monitoring,<sup>51</sup> is available and following counselling on the cost and potential risk of multiple pregnancy.

Another study conducted to compare FSH and laparoscopic ovarian drilling (LOD) with high-quality evidence found no difference in clinical pregnancy rate, live birth rate, miscarriage, or ovulation rate, but LOD was better than gonadotropins for multiple pregnancy rate OR: 0.13 (0.03-0.59), 4 studies, 303 participants.<sup>56</sup>

### Laparoscopic Ovarian Drilling

Laparoscopic ovarian drilling has been another successful second-line treatment for ovulation induction in clomiphene-resistant cases of PCOS as an alternative to gonadotropin therapy.<sup>52,57</sup> Laparoscopic ovarian drilling was found to have advantages like repeated mono-ovulatory cycles that reduces the risk of multiple pregnancy and OHSS; therefore, it does not require intensive monitoring.<sup>52</sup> Also with avoidance of untoward peripheral antioestrogenic effects of clomiphene on endometrium and cervical mucus, it improves pregnancy rates. In clomiphene-resistant cases, LOD leads to normalisation of serum LH and androgens which also significantly reduces miscarriage rates.<sup>57</sup>

However, the disadvantage is needing a general anaesthetic, the risk of postoperative adhesions and premature ovarian failure, and more importantly the risk of surgical intervention and perioperative complications in women particularly those who

are overweight or obese. These factors should be considered before choosing this option. Cleeman et al<sup>58</sup> reported a pregnancy rate of 61%, where<sup>59</sup> LOD was performed as a first-line therapy in PCOS women or where laparoscopy is needed to assess pelvis or for women who cannot attend to intensive monitoring needed in gonadotropin therapy.

Bayram et al<sup>60</sup> conducted a randomised multicentre study, and the cumulative pregnancy rate after 6 months after LOD was found to be 34%, whereas it was almost double with the FSH stimulation at 67%. After 12 months, the results and success with each group were comparable. It demonstrated an OR: 1.01, 95% CI: 0.81 to 1.24. In addition, patients allocated to have LOD had a significantly lower risk of multiple pregnancy with OR of 0.11, and CI of 0.01 to 0.86.

Amer et al<sup>61</sup> described 4-point cauterisation of the ovarian capsule, each for 4 second, at 40W and for a depth of 4 mm with a mixed current in monopolar electrosurgical needle. This restored the ovarian activity and reduced the testosterone and LH levels.<sup>58</sup>

However, this fixed thermal dosage may not induce optimal ovulation in some women especially with large ovaries.<sup>61</sup>

It is very important to use the minimum effective intervention or dose to have an optimum ovulation rates but reduce the risk of ovarian damage and its effect on ovarian reserve and future periovarian adhesions formation. A surgeon with expertise in laparoscopic surgeries should perform the procedure.<sup>58</sup>

## Assisted Reproductive Technology

### *In vitro fertilisation*

In vitro fertilisation is considered as a third-line treatment option for anovulatory PCOS with no other cause of infertility, if first- or second-line ovulation induction treatments are unsuccessful. Although, IVF is a highly effective treatment with pregnancy rates reaching up to 50% from a single treatment cycle, especially in young women with a good ovarian reserve, there remain significant challenges with this treatment modality. These include the high risk of OHSS, multiple births, accelerated endometrial maturation along with high cost, and variable access to treatment.

Women with PCOS are at a greater risk of a high response to controlled ovarian hyperstimulation (COH) and development of OHSS. The use of the GnRH antagonist protocol rather than the long agonist protocol has demonstrated a significant decrease in the incidence of OHSS as detailed in a systematic review by Pundir et al<sup>62</sup> and a more recent review by Teede et al.<sup>63</sup> A more important aspect of the use of the GnRH antagonist protocol is that it allows GnRH agonist to be used as the final maturation trigger rather than HCG. A Cochrane review (2014) which includes 5 RCTs, demonstrates a reduction in the incidence of mild, moderate, and severe OHSS with the use of the GnRH agonist trigger as compared to HCG (OR: 0.15, 95% CI: 0.05-0.47; 8 RCTs, 989 women,  $I^2 = 42%$ , moderate-quality evidence).<sup>64</sup> The use of the GnRH agonist trigger reduced the risk of OHSS in autologous treatment

cycles with a fresh embryo transfer to the detriment of ongoing pregnancy rates, OR: 0.70, 95% CI: 0.54 to 0.91; 11 studies, 1198 women,  $I^2 = 59%$ , low-quality evidence, and higher early miscarriage rates (OR: 1.74, 95% CI: 1.10-2.75; 11 RCTs, 1198 women,  $I^2 = 1%$ , moderate-quality evidence) attributed to undesirable effects on the endometrium.<sup>65</sup> This can be overcome by the concept of cycle segmentation and an elective freeze-all policy in those having a GnRH agonist trigger. There is insufficient evidence for the use of any specific type of FSH or the use of adjunct LH for COH during IVF.<sup>64</sup> The use of metformin as an adjunct during IVF was found to decrease the incidence of OHSS (OR: 0.29, 95% CI: 0.18-0.49, moderate-quality evidence).<sup>65</sup> These developments have made it possible to control with greater efficacy the deleterious effects of gonadotropins in women with PCOS in an IVF cycle. The introduction of the elective single embryo transfer (eSET) policy in IVF treatment for younger women has significantly reduced the incidence of multiple births following IVF.<sup>66</sup> Thus, the use of the GnRH antagonist protocol, GnRH agonist trigger, an elective freeze-all policy, and the use of eSET have made IVF a much more effective and safe treatment for women with PCOS.

The comparative efficacy of IVF has never been compared to ovulation induction treatments, especially in terms of outcomes such as time to pregnancy (which is a very important outcome as perceived by patients), pregnancy rates, multiple pregnancy rates, and incidence of OHSS. These interventions have also never been compared in a health economic evaluation or in terms of the HQoL of women undergoing treatment.

### In Vitro Maturation

In vitro maturation involves the retrieval of immature oocytes from unstimulated or minimally stimulated ovaries. This treatment modality has been suggested for women with PCOS to eliminate or reduce the risks of OHSS following COH. There are no reported RCTs to compare these 2 interventions in terms of the desired outcomes. All available evidence is from retrospective studies with conflicting results. Tannus et al<sup>67</sup> conducted a retrospective study in 159 patients with PCOS and found excellent pregnancy rates of 44.7% and live birth rate of 34.6 % in women.<sup>68</sup> In 2 different studies done by Child<sup>68</sup> in 2002 and Greameau et al in 2012<sup>69</sup>, which compared the outcomes of IVM and IVF, IVM demonstrated low implantation rates.<sup>70,71</sup> The lower implantation rates through IVM may be due to a reduced oocyte potential, higher frequency of abnormal meiotic spindle, and chromosomal alignment.<sup>72</sup>

No adverse effects on offspring have been reported following IVM.<sup>72</sup> In vitro maturation is labour intensive, time-consuming, and needs specialised treatment experience. Hence, this may be offered in centres with sufficient expertise.

## Conclusion

Polycystic ovary syndrome is a multifaceted condition. Hence, when choosing an effective treatment option for the woman with PCOS, a holistic approach plays an important role. A

multidisciplinary care addresses not only subfertility or anovulation but also metabolic and psychological issues that are often associated within its spectrum. A holistic care enables clinicians to avoid missing any opportunity to prevent, treat, and optimise health, so as to prevent future complications and increase success rates of fertility treatments.

The methods like pharmacological options and IVF are routinely offered in the fertility centres. However, lifestyle modifications like diet, exercise, and behavioural therapy are principle treatment in most.

In pharmacological methods, letrozole is now the first-line treatment to induce ovulation in anovulatory women with higher success and low complication rates compared to clomiphene. Metformin is generally used as an adjunct to other oral agents to induce ovulation and as an insulin sensitiser to affect metabolic aspects of PCOS. Low-dose gonadotropins are used as a second-line agent to avoid invasive procedure like IVF or can be used as a first-line agent when monitoring, affordability, and accessibility are not a major issue. The third-line treatment consists of IVF/intracytoplasmic sperm injection (ICSI), which is more invasive but is indicated when the previous interventions have failed or can be offered as a treatment of first choice in selective causes that impair the occurrence of natural pregnancy, like tubal occlusion or male factor.

### Author Contributions

SS and PB conceived the manuscript. SS drafted the manuscript and did the literature search. All authors contributed to all versions of the manuscript.

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