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Polycystic Ovary Syndrome: Fertility Management

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Abstract Polycystic ovary syndrome (PCOS) is characterized by a series of symptoms, including oligomenorrhea or amenorrhea anovulation or infertility; it is associated with insulin resistance and compensatory hyperinsulinemia. Several treatment options are available for women with anovulatory infertility related to PCOS. Clomiphene citrate (CC) is the first-choice for induction of ovulation in PCOS patients. Laparoscopic ovarian drilling (LOD) or gonadotropin ovarian stimulation can be offered after failure of CC to achieve pregnancy. Hyperinsulinemia related to PCOS can be corrected by weight loss or insulin-sensitizing agents, such as metformin, which alone or in combination with other agents are capable of restoring ovulation. Only very limited clinical data are available on the use of letrozole at present, so letrozole cannot be recommended for routine use in ovulation induction. When all treatments fail, in vitro fertilization and embryo transfer (IVF/ET) can be tried and can have excellent results. Many treatment options available today ensure that the majority of women who are subfertile due to PCOS can be treated successfully.

Keywords Polycystic ovary syndrome · PCOS · Anovulation · Infertility · Clomiphene citrate · Laparoscopic ovarian drilling · Oligomenorrhea · Female infertility · Hyperinsulinemia · Hyperandrogenism · Aromatase inhibitors · Gonadotropin therapy

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Introduction

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder affecting 6–8 % of women of reproductive age and is the most common cause (75 %) of anovulatory infertility [1–4]. The majority of women with anovulation or oligo-ovulation due to PCOS have menstrual irregularities, associated with clinical or biochemical evidence of hyperandrogenism. Making the diagnosis of PCOS is important, because this will dictate the treatment plan. Before making therapeutic decisions, patients should undergo routine examination to assess (usually by blood sample) luteinizing hormone (LH), follicle stimulating hormone (FSH), total testosterone and fasting glucose, and insulin concentrations. The ratio of fasting glucose to insulin levels gives a good indication of insulin sensitivity [5], because hyperinsulinemia is present in approximately 80 % of obese women and 30–40 % of women of normal weight with PCOS [6] and is strongly associated with anovulation. It is useful to know this ratio for possible therapeutic intervention. The LH value can be expected to be high in 40 % of women with PCOS and is thought to be detrimental to successful ovulation induction and to the incidence of miscarriage [7]. A semen analysis is mandatory before starting treatment; moreover, tubal assessment should be performed when indicated.

There are several modes of inducing ovulation for these patients. Because hyperinsulinemia, lack of sufficient endogenous FSH activity, and high LH concentrations can all be instrumental in the pathology of anovulation in PCOS, the treatment modes described

basically depend on reducing insulin concentrations, FSH stimulation of the ovaries, reducing LH concentrations, or a combination of these.

Weight Reduction

Obesity occurs in 50–65 % of women with PCOS; the majority has central body fat distribution and an increased waist-to-hip ratio. Central obesity and BMI are major determinants of insulin resistance, hyperinsulinemia, and hyperandrogenemia. The rate of insulin resistance in women with PCOS is 50–80 %, and a large majority of these women are obese [5, 8]. In addition, obesity is associated with early pregnancy loss and late pregnancy complications.

For obese women with PCOS, a loss of just 5–10 % of body weight is enough to restore reproductive function in 55–100 % within 6 months of weight reduction [9–13]. Moreover, it can improve the metabolic profile of obesity and reduces the development of type 2 diabetes in large randomized trials [14••]. Weight loss has the undoubted advantage of being effective and cheap, with no side-effects, and should be the first line of treatment in obese women with anovulatory infertility associated with PCOS. Several approaches are available for weight reduction, including diet, exercise, drugs, and surgery.

However, no large, randomized, controlled trials have evaluated the effectiveness of restoration of reproductive potential by lifestyle modification. Nevertheless, cultivation of healthy eating patterns and adequate exercise is prudent advice for any healthy individual, including obese women with PCOS.

Clomiphene Citrate

Clomiphene citrate (CC) has long been the first line of treatment for PCOS women with absent or irregular ovulation. It is a nonsteroidal, synthetic estrogen, which is related to the synthetic estrogen, and is known for its anti-estrogenic and weak estrogenic properties. By binding to estrogen receptors at the hypothalamic–pituitary level, clomiphene blocks the negative feedback effect of estradiol on GnRH secretion, thus resulting in an increase in the GnRH pulse amplitude leading to an increased gonadotropin secretion from the pituitary. The resultant increase of FSH triggers an ovulatory cycle.

The initial dose of clomiphene is most often 50 mg per day administered orally for 5 subsequent days, usually starting from day 2–3 [15] or day 3–5 [16] from the beginning of the menstrual cycle. In patients resistant to standard doses, clomiphene therapy should be prolonged to 8 days [17], or a standard drug dose should be increased to 150 mg or even 200 mg per day [18]. The ovulation rate is approximately 80 % [19] and the pregnancy rate is 35–40 % within 6 cycles [20]. Once ovulation has been achieved on a certain dose, treatment is continued with that dose for 6–12 months. Provided that all other subfertility factors have been excluded, the cumulative conception rate with CC continues to increase until it reaches a plateau at treatment cycle 12. Prolonging clomiphene treatment beyond 12 cycles has been linked with an increased risk of borderline or invasive ovarian tumor [21] and should, therefore, be discouraged.

Additionally, approximately 20–25 % of anovulatory women with PCOS will not respond at all to clomiphene citrate and are considered to be “clomiphene-resistant” [22]. Patients who do not respond to clomiphene are likely to be more obese, insulin–resistant, and hyperandrogenic than those who do respond. It disclosed that only the coadministration of clomiphene and dexamethasone improved significantly the pregnancy rate of these patients. Combined treatment with oral contraceptives and clomiphene also has been proved successful, whereas other combinations did not increase significantly the pregnancy rate in clomiphene-resistant patients [23].

Although evidence from recent large trials does not support the use of ultrasound monitoring, it is recommended to monitor the first cycle to allow adjustment of the dose in subsequent cycles and to exclude multifollicular development. There is no evidence that administration of human chorionic gonadotropin (hCG) in midcycle after CC improves the chances of conception. Age and duration of infertility are the most important determinants of the probability of conception [24•]. The younger the patient and the shorter the duration of her infertility, the higher are her chances of conceiving. Other important factors determining the chances of pregnancy are the dose and duration of CC. Most pregnancies (50 %) occur with CC 50 mg and only approximately 10 % occur with 150 mg. Drawbacks of CC treatment are associated with a miscarriage rate of up to 40 %, increased risk of multiple pregnancies, and a small risk of ovarian hyperstimulation syndrome (OHSS).

Aromatase Inhibitors

Aromatase inhibitors have been investigated recently as potential alternatives to CC for induction of ovulation. Letrozole is the most prevalently used antiaromatase for this indication; it is currently licensed for use in postmenopausal patients with advanced breast cancer to suppress estrogen production, using letrozole ovulation required the patient fully informed consent. It inhibits estrogen production in the hypothalamus–pituitary axis, which implies an increase in gonadotropin-releasing hormone (GnRH) and FSH. There is a relative decrease in aromatase in women with

PCOS, which reduces the production of follicles responsible for effective ovulation.

Letrozole has been used as a single agent or an adjuvant to FSH therapy in a daily dose of 2.5, 5, or 7 mg, although the optimal dose remains unknown. It is given for 5 days during the early follicular phase.

However, in a prospective, randomized trial comparing letrozole with clomiphene, pregnancy rates were similar. Theoretically, letrozole offers several advantages over CC. In contrast to CC, letrozole does not cause estrogen receptor downregulation. Letrozole treatment could, therefore, avoid the anti-estrogenic adverse effects known to occur with CC on the quality and quantity of cervical mucus and on endometrial development. Consequently, letrozole treatment may overcome the problems associated with CC treatment, including a discrepancy between ovulation and conception rates and a higher than expected incidence of miscarriage in conception cycles. In addition, unlike CC, which accumulates in the body because of its long half-life, letrozole is eliminated from the body rapidly (half-life of 45 hours). The rapid elimination and reversibility of letrozole may allow the endometrium to respond well to rising estrogen levels in the late follicular phase. The rising estrogen levels in the late follicular phase also may result in a negative feedback reduction of FSH resulting in a shorter FSH window. This in turn will result in a monofollicular ovulation with a reduction of multiple pregnancy rates.

Surgical Treatment

Laparoscopic ovarian drilling (LOD) is the surgical treatment for clomiphene resistance in women with PCOS, and it also is a useful therapy for anovulatory women with PCOS who fail to respond to clomiphene and need a laparoscopic assessment of their pelvis [25]. It is free of the risks of multiple pregnancy and ovarian hyperstimulation and does not require intensive ultrasound monitoring. Therefore, people who live too far from the hospital and who are unable to attend the intensive monitoring are contraindicated. Furthermore, ovarian drilling appears to be as effective as routine gonadotrophin therapy for the treatment of clomiphene-insensitive PCOS and is less costly. Women with polycystic ovaries who have overresponded to superovulation for in vitro fertilization (IVF) are subjected to ovarian drilling as a way to reduce the likelihood of subsequent OHSS [26]. If one accepts that appropriately performed ovarian drilling by sensitizing the ovary to FSH and ovarian diathermy certainly makes the clomiphene-resistant polycystic ovary sensitive to clomiphene.

Several techniques of laparoscopic ovarian surgery have been described with comparable success rates. LOD, which is a widely used technique, is performed by using a monopolar diathermy needle to penetrate the ovarian capsule at a number of points. The site of application should be away from the ovarian vessels and the fallopian tube. As the needle is pushed into the ovarian capsule, electricity is activated for 5 s by using a monopolar coagulating current set at 30 W. Gjoannaess [27] cauterized each ovary at five to eight points, for 5–6 seconds at each point with 30–40 W, and resulted in ovulation in 90 % and conception in 69 % of the 35 women who were involuntarily infertile.

Selection of patients for LOD PCOS women with marked obesity (BMI $\geq$35 kg/m^2), marked hyperandrogenism (testosterone $\geq$4.5 nmol/l), or long duration of infertility (>3 years) in PCOS appear to be resistant to LOD. It is, therefore, recommended that alternative methods of treatment should be considered for this group of patients. On the other hand, high pretreatment serum LH concentrations in LOD responders appear to predict higher probability of pregnancy. The risks of LOD are minimal and include the risks of laparoscopy, adhesion formation, and a theoretical risk of excessive ovarian damage leading to ovarian failure. It is important to keep the number of punctures to the minimum.

Recently, Fernandez et al. [28, 29] reported the feasibility of ovarian drilling by transvaginal laparoscopy (THL) for PCOS with a 5-Fr bipolar needle. They performed ovarian drilling by THL in 80 CC-resistant anovulatory women with PCOS. During a mean follow-up of 18.1 months, 73 (91 %) patients recovered regular ovulatory cycles. The cumulative pregnancy rate was 60 % for spontaneous and stimulated cycles, with 40 % imputed to drilling alone. The present study demonstrated that THL for ovarian drilling offers a valuable, effective, and less invasive alternative to the standard laparoscopic procedure in patients with clomiphene-resistant PCOS. Because of the procedure of THL is in a saline environment, it significantly reduced incidence of adhesions. However, the number of ovarian drilling through THL is needs further study of large samples.

Gonadotropin Therapy

Gonadotropin therapy is widely used as the second-line treatment for induction of ovulation after failure of CC to achieve pregnancy (there is no response to clomiphene in a daily dose of 150 mg or 4–6 ovulatory cycles have not resulted in a pregnancy) in anovulatory women with PCOS. Polycystic ovaries contain double the usual number or more small antral follicles, all sensitive to FSH stimulation, as in the normal ovary [30]. This makes anovulatory women with PCOS who receive gonadotrophins particularly prone to multiple follicular development; then ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies occur. As a result of this hypersensitivity, the conventional high-dose

(150 IU) protocol, which has been in use since the 1970s, was associated with an unacceptable rate of OHSS in women with PCOS. This regimen, therefore, has been largely replaced by low-dose (37.5–75 IU/day) treatment regimens, which could be applied in a step-up or step-down. The goal of this approach is to allow FSH to rise slowly just above the FSH threshold while avoiding an excessive ovarian response, thus minimizing the risks of OHSS and multiple pregnancies.

The chronic low-dose, step-up gonadotropin regimen is the recommended protocol for ovulation induction in PCOS women. This approach is characterized by a small starting daily FSH dose (typically 50–75 IU), which is continued for a long period (14 days) without any dose changes and then increased gradually, if necessary, by 50 % of the initial dose (25–37.5 IU) every 7 days, until a dominant follicle emerges (not exceeding 28 days). A comparative prospective study of the conventional regimen with chronic low-dose administration of FSH for anovulation associated with PCOS [31] involved 50 participants treated with FSH, half of them using a conventional stepwise protocol and half with a regimen of chronic low dose as described above. This approach seems to give the best result with high rates of monofollicular ovulation (70 %) and low rates of multiple pregnancies (5 %) and OHSS (<1 %) while maintaining good pregnancy rates (20 % per cycle and 40 % per patient) [32]. Reduction of the 14-day initial period to 5–7 days is associated with higher rates of multiple pregnancy and OHSS.

The step-down approach applies a high starting dose that continues until ovarian response is established. The FSH dose is then reduced in small decremental amounts in two steps. Therapy usually commences with 150 IU FSH per day, reduced by one decrement (37.5 IU) when one follicle has been selected (10 mm) with a further reduction 3 days later by another decrement to 75 IU per day, which is then continued until the day of hCG injection [33, 34]. The aim of this approach is to mimic the physiological FSH threshold concept of the normal ovulatory cycle, which is characterized by an intercycle FSH elevation above the threshold for approximately 5 days (the window) to allow the selection of one leading follicle, followed by a gradual decline of FSH with the emergence of the dominant follicle, which is increasingly FSH-independent. The advocates of this approach claim that it is as successful as the chronic low-dose, step-up protocol in achieving monofollicular development and that it has the advantage of reducing the duration of the treatment.

However, the largest study published so far has shown that the step-up regimen is safer in terms of monofollicular development. The step-down approach requires more stringent follicular monitoring than the step-up regimen.

GnRH Agonists

The ability of GnRH agonists to suppress LH concentrations before and during ovarian stimulation has earned them an undisputed place in IVF treatment protocols. They confer the advantage of eliminating, almost completely, the annoying occurrence of premature luteinization. In addition, some investigators have reported more pregnancies, possibly better quality eggs, and fewer miscarriages [35]. Their possible application during ovulation induction therefore should be particularly relevant in the presence of the chronic high serum concentrations of LH observed in a high proportion of women with PCOS. Theoretically, by suppressing LH concentrations, GnRH agonists should eliminate premature luteinization and alleviate the relatively low pregnancy rates and the high miscarriage rates witnessed in this group of patients [36].

Why, then, has the GnRH agonist not become standard treatment for ovulation induction in PCOS, given the fact that our experience and that of others has shown an increased pregnancy rate and lower miscarriage rate in women receiving combination treatment of agonist and gonadotrophins when LH concentrations are high? Probably because co-treatment with GnRH agonist and low-dose gonadotrophin therapy are more cumbersome, longer, requires more gonadotrophins to achieve ovulation, and has a greater prevalence of multiple follicle development. Combining GnRH agonist with gonadotrophin stimulation will exacerbate the problem of multiple follicular development and therefore increase rates of cycle cancellation, OHSS, and multiple pregnancies [37, 38]. The loss of the endogenous feedback mechanism when using GnRH agonist and the need for greater stimulation of follicles by the larger amounts of gonadotrophins are probably responsible for the fact that GnRH agonists are not the solution to the problem of multiple follicular development.

To overcome the two main complications of ovulation induction for PCOS—multifollicular development and the possible deleterious effects of high LH levels, low conception rates, and high miscarriage rates—a combination of chronic low-dose FSH stimulation with GnRH agonist therapy should theoretically yield the best results. Scheele et al. [39] studied women with PCOS undergoing ovulation induction with chronic low-dose FSH therapy, with and without adjuvant GnRH agonist therapy. A very low rate of monofollicular ovulation was achieved (14 %) in the agonist cycles compared with 44 % of those treated with low-dose FSH alone. Treatment with GnRH agonist abolished neither the inter- nor intraindividual variability of the FSH dose required to induce ongoing follicular growth but also seemed to induce an even further increase in the sensitivity of the PCO follicles to gonadotrophin stimulation once the threshold FSH dose had been reached.

Gonadotrophin-Releasing Hormone Antagonists

There are several theoretical advantages over gonadotrophin-releasing hormone antagonists because they act by the mechanism of competitive binding, which allows a modulation of the degree of hormonal suppression by adjustment of the dose. Furthermore, antagonists suppress gonadotrophin release within a few hours, have no flare-up effect, and gonadal function resumes without a lag effect following their discontinuation. If we apply these advantages to an ovulation induction protocol for PCOS, one can visualize that, used in combination with low-dose FSH administration, the antagonist could be given in single or repeated doses when a leading follicle of 13–14 mm is produced. This would theoretically prevent premature luteinization, protect the oocyte from the deleterious effects of high LH concentrations, and still allow the follicle to grow unhindered to ovulatory size. Compared with agonist-treated cycles, this would confer the advantages of a much shorter cycle of treatment, promise more conceptions and fewer miscarriages, reduce the amount of gonadotrophin required, and increase the incidence of monofollicular ovulation with a consequent reduction in the prevalence of OHSS and multiple pregnancies.

To date, one trial employing a GnRH antagonist with recombinant FSH, specifically for women with PCOS, has been published [40]. Following pretreatment with oral contraceptives, a GnRH antagonist was started in 20 patients on day 2 of the cycle. When LH concentrations were found to be suppressed, concurrent antagonist and recombinant FSH therapy was started and continued until the day of hCG. LH was effectively suppressed by one dose of antagonist, and all patients ovulated. Overall clinical pregnancy rates were 44 % and ongoing pregnancy rates were 28 %. This was a preliminary trial, and large, randomized, controlled trialss are needed to confirm these results.

Metformin

Metformin is a biguanide currently used as an oral antihyperglycemic agent and approved by the United States Food and Drug Administration (FDA) to manage type 2 diabetes mellitus. The use of metformin is associated with increased menstrual cyclicity, improved ovulation, and a reduction in circulating androgen levels [41]. Metabolic benefits are enhanced in the presence of weight loss, and weight loss itself may be enhanced in the presence of metformin. Its primary clinical action is to inhibit hepatic glucose production, although it also decreases intestinal glucose uptake and increases insulin sensitivity in peripheral tissues [42]. Metformin likely plays its role in improving ovulation induction in women with PCOS through a variety of actions, including 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.

Metformin should be started at a low dose, with gradual dose escalation, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required to achieve regular ovulatory cycles. The usual starting dose is 500 mg once a day given with meals. Dosage increases should be made in increments of 500 mg weekly, not exceeding a maximum dose of 2,550 mg per day, given in divided doses. Patients should be warned against excessive alcohol intake while receiving metformin, because this could precipitate lactic acidosis.

The restoration of regular menstrual cycles by metformin has been reported in the large majority of published series, and the reinstatement of ovulation occurred in 78–96 % of patients [43–48]. Fleming et al., in the largest, randomized, controlled trial published to date, demonstrated a significantly increased frequency of ovulation with metformin compared with placebo in a group of 92 oligomenorrheic women with PCOS. In a randomized, controlled trial performed on clomiphene-resistant, infertile patients with PCOS, compared with placebo, metformin markedly improved ovulation and pregnancy rates with clomiphene treatment [49]. Not only does metformin seem to be safe when continued throughout pregnancy, but preliminary data strongly suggest that this strategy can severely decrease the high miscarriage rate usually associated with PCOS [50, 51]. However, a recent meta-analysis showed that metformin had no effect on the miscarriage risk in PCOS patients when administered before pregnancy [52]. It is hoped that the apparent lack of teratogenicity and beneficial effect of metformin on miscarriage rates will be confirmed by future studies.

In vitro Fertilization and Embryo Transfer

The last possibility to achieve a full-term pregnancy in women with PCOS is to use in vitro fertilization (IVF) techniques [53]. Patients with PCOS are characterized by anovulatory cycles that conceptually are not an indication for IVF techniques. These techniques are used as a last resort when treatments with CC, gonadotropins, and letrozole have failed. IVF is the first choice in cases of concomitant diseases both in women (severe endometriosis, tubal obstruction, etc.) and men (azoospermia, male factor). In vitro maturation of oocytes from women with PCOS may become a possible option [54]. However, it is proving to be technically difficult at present and concerns about the well-being of pregnancies achieved from IVF have not yet been fully answered.

Conclusions

Women with PCOS often present with anovulatory infertility, menstrual irregularities, and obesity. Anovulatory PCOS women who are overweight or obese should first be encouraged to lose at least 5–10 % of their weight before embarking on medical treatment. CC remains the standard first-line treatment for ovulation induction in patients with PCOS. LOD or gonadotropin therapy could be offered as the second line of choice for induction of ovulation in CC-resistant PCOS women. The chronic low-dose protocol is the recommended protocol for gonadotropin-based ovulation induction in anovulatory PCOS due to the high mono-ovulation rate achieved by this approach. At present, metformin and letrozole cannot be recommended for routine use in ovulation induction either alone or in combination with other agents; it needs the informed consent of the patient. When all of the above fails, we can consider the IVF-ET.

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- • Of importance,
- •• Of major importance

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