Management of Anovulatory Infertility Associated with Polycystic Ovary Syndrome (PCOS)

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Polycystic ovary syndrome (PCOS) is the most common cause of anovulatory infertility and it appears to be difficult to induce the ovulation safely and successfully. Anovulation in PCOS is exacerbated by weight gain and improved by lifestyle modification and weight reduction. If these measures are not successful, conception can usually be achieved with the use of clomiphene citrate, metformin alone or in combination with clomiphene citrate, gonadotrophins, surgical ovulation induction using laparoscopically applied techniques to the ovaries and assisted reproductive techniques. One of the main goals of ovulation induction is to avoid multiple follicular developments that may result in overstimulation, leading to cycle cancellation and complications such as multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). Fertility can usually be restored by appropriate choice of induction of ovulation, but careful monitoring is required.

Keywords: *PCOS, Anovulatory infertility*

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In women of reproductive age, polycystic ovary syndrome (PCOS) is estimated to be the most common cause of endocrine disorder with an incidence of 5-10% and also the most common cause of anovulatory infertility[1,2]. PCOS is a complex, heterogeneous endocrine disorder which needs the criteria for diagnosis. The recent consensus conference concluded that any two out of the three parameters (polycystic ovary appearance at ultrasound examination, hyperandrogenism-clinical or biochemical, and oligo-amenorrhea) with the exclusion of other causes of hyperandrogenism such as adult-onset congenital adrenal hyperplasia, hyperprolactinemia and androgen-secreting neoplasms was sufficient to diagnose PCOS[3].

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The cause of infertility in patients with PCOS is generally lack of ovulation because of a failure of the follicles to develop beyond 10 mm. Because the primary cause of PCOS is still unknown, management of anovulatory infertility associated with this syndrome is based on the overall clinical picture, which includes variables such as age, duration of infertility, degree of the ovarian and adrenal androgen excess, overweight and insulin resistance problems. Meticulous evaluation and examination to establish a differential diagnosis of PCOS before initiating the treatment is very important[4]. This approach is recommended to rule out other disorders potentially problematic for the woman's general health and for optimizing her chances of achieving successful pregnancy by using the appropriate intervention.

Lifestyle modification and weight loss have been suggested as the first line of therapy to induce ovulation in these women before considering medical therapy in order to improve the chance of a successful outcome[2,4,5]. Induction of ovulation is the next step which may include medical therapy (alone or combined with other drug therapies and/or interventions) or surgical procedures[2]. Among all approaches to ovulation induction, drug therapy remains the most common and is primarily indicated for reproductive-aged women with anovulatory infertility. Women with PCOS considering ovulation induction to manage their anovulatory infertility should be aware that: regardless of

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the approach used, they appear to be at increased risk for multifollicular development and spontaneous abortion; the risk of developing serious complications such as multiple pregnancies and ovarian hyperstimulation syndrome appears to be higher when gonadotrophin therapy is used. Data on the overall cost of using various approaches to ovulation induction are needed to aid in the couple's decision-making and to assist in the formulation of policy for using this therapy to manage this indication. Currently, many approaches to ovulation induction are in widespread use for this indication. However, none of these therapies has become unique in achieving pregnancy safely in all cases. Methods of ovulation induction for anovulatory infertility associated with PCOS were discussed in this review.

Lifestyle modification and weight loss

The most important initial step in ensuring an optimal response to induction of ovulation is dietary and lifestyle modification. For women with PCOS, central obesity and BMI are major determinants of insulin resistance, hyperinsulinemia and hyperandrogenemia. The rate of insulin resistance is 50-85% and a large majority of these women with PCOS are obese[6]. Obese women with PCOS have shown the resumption of ovulation and improvement of hyperandrogenism from weight loss alone, largely related to the amelioration of obesity-related hyperinsulinemia[7], and also the improvement of successful pregnancy[8,9]. Therefore, weight loss should be seriously pursued in most cases of PCOS associated with obesity before starting ovulation induction. In such cases, even the loss of less than 5% of body weight often leads to the restoration of normal cycles, especially if a sustainable program of dietary changes and exercise is implemented[10]. Even if a patient's ovulatory dysfunction persists after weight loss, it can be expected that she will be more likely to have a favorable response to fertility treatment [9]. Furthermore, once conception does occur, obesity-related complications of pregnancy will be less likely. Weight loss has the undoubted advantages 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. However, weight control is difficult to maintain. For women who fail to lose weight, normal weight women who suffer from hyperinsulinemia and its consequences, and when weight loss fails to restore ovulation, medical ovulation induction is the next suggested step[4,5].

Medical ovulation induction

Medical ovulation induction allows women to ovulate and have the chance of conceiving naturally. The principle of this treatment is to stimulate the ovaries to produce a single mature (dominant) follicle, to induce ovulation, and to allow fertilization and pregnancy to occur by natural intercourse. The main steps include: proper and comprehensive diagnostic evaluation and clinical examination of the potential candidate to establish a correct and differential diagnosis, and exclude other disorders and possible causes of anovulation and infertility; correcting any underlying factors, if present, and optimizing health before commencing ovulation induction; provision of appropriate medication to stimulate one single egg or ovum to mature; close and careful monitoring of the treatment cycles (by ultrasonography and/or biochemical tests) to examine the ovarian response, individualize drug doses and prevent side effects and complications; administration of ovulation triggers (timed by ultrasonography with respect to the size and number of developing follicles), where appropriate, to cause the final maturation and release of one egg; sexual intercourse, timed to coincide with the treatment-induced ovulation; and pregnancy testing.

One of the main goals of medical ovulation induction is to avoid multiple follicular developments that may result in overstimulation, leading to cycle cancellation and complications such as multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). Polycystic ovaries (PCOs) appear to be highly sensitive to the ovulation inducing agents currently available and have a tendency toward multiple follicular recruitment. A variety of ovulation inducing drugs have been used in these women, but none of them are unique in terms of safety and efficacy in achieving pregnancy. The syndrome's heterogeneity is reflected in the different responses to the various ovulation inducing drugs: the elevated LH levels (present in ~40% of women with PCOS) may adversely affect the outcome of treatment by reducing the conception rate and increasing the spontaneous abortion/miscarriage rate; the hyper-androgenic state may also adversely affect the response to treatment; obesity and insulin resistance may result in hyperandrogenism and cause poor response; ovulation inducing drugs appear to be less effective when BMI > 28-30 kg/m^2; insulin resistance and the compensatory hyper-insulinemia may increase the risk for OHSS; and the polycystic ovaries may be resistant to drugs even after the administration of relatively high doses of

medication[11].

Clomiphene citrate (CC)

The initial step for induction of ovulation is anti-estrogen therapy. The most commonly used agent is clomiphene citrate (CC). Tamoxifen, another anti-estrogen agent, has also been used for this purpose but less frequently. CC is given orally, usually at a starting dose of 50 mg/day for 5 days, generally starting on day 2 or 3 after the onset of spontaneous or progestin-induced menses, raising the dose in increments of 50 mg/day each cycle until an ovulatory cycle is achieved (no advantage in using a daily dose of more than 150 mg). The drug stimulates endogenous FSH secretion, leading to development of a dominant follicle. The final activity of CC may be influenced by many factors such as woman's age, metabolism, dosage regimen, administration period relative to the cycle, cause of anovulation, and estrogenic state, as well as carry-over effects from previous CC cycle(s), and effects of unknown metabolites[14]. Although there currently are no data to reliably predict response to CC in these women, it appears that the efficacy of CC therapy is decreased in the presence of obesity, hyperandrogenemia, elevated testosterone concentrations and severe insulin resistance[12]. Although 70-80% of PCOS women can ovulate by the treatment with CC, only 40%of the PCOS women become pregnant [13]. The lower pregnancy rate in relation to ovulation rate has been attributed to the anti-estrogenic effects of CC and its metabolites on the cervical mucus, the endometrium and possibly the oocytes. Women who do not ovulate with increasing doses of CC are described as "CC-resistance" and remain a major challenge in gynecologic endocrinology. The reason for resistance to CC is poorly understood. Patients who do not respond to CC are likely to be more obese, insulin resistant and hyperandrogenic than those who respond[14,15].

Adjuvant therapy with CC

Dexamethasone Daily doses of dexamethasone, 0.5 mg at bedtime, as an adjunct to CC therapy, suppress the adrenal androgen secretion and may induce responsiveness to clomiphene in previous non-responders, mostly hyperandrogenic women with PCOS and elevated concentrations of dehydroepiandrosterone sulphate (DHEAS)[16]. Although this method obtains some success, medium to long term glucocorticoid steroid therapy often induces side effects including increased appetite and weight gain which is not an appealing proposition for women with PCOS.

Contraceptive pills/GnRH agonist Contraceptive pills reduce the high serum LH and androgen levels which contribute to the lack of ovarian response to ovulation inducing agents. When contraceptive pills are used for 6 months followed immediately by resumption of CC administration, a better response might be obtained[17]. GnRH agonist/oral contraceptive combination is effective in lowering serum LH levels and reducing hyperandrogenism and hirsutism in patients with PCOS[18].

Bromocriptine Successful induction of ovulation and achievement of pregnancy with bromocriptine can occur in the absence of galactorrhea and with normal prolactin levels in women who failed to respond to CC[19].

Metformin Metformin, an insulin sensitizing agent, has been used as an adjuvant to enhance CC response in these women.

Insulin sensitizing agents

Two different types of insulin-sensitizing agents have been used, metformin, a biguqnide, and the thiazolidinediones including troglitazone, rosiglitazone, and pioglitazone. More data is available on metformin, whilst troglitazone has been withdrawn from the market because of liver toxicity. The newer thiazolidinediones have lower toxicity but have not been extensively evaluated in PCOS.

Metformin

Metformin is an oral biguanide, well established for the treatment of hyperglycaemia, that does not cause hypoglycaemia in normoglycaemic patients. Several studies on the effect of metformin in women with PCOS have demonstrated a significant improvement in insulin concentrations, insulin sensitivity, and serum androgen concentrations accompanied by decreased LH and increased SHBG concentrations[20]. The restoration of regular menstrual cycles and the return of ovulation occurred in 78%-96% of patients by metformin[20,21].

Metformin is administered in a dose of 500-1700 mg daily. A supervised incremental dosage protocol of metformin therapy has been commonly used. Durign the first week, PCOS patients take 500 mg metformin once daily wit meals, and this introductory phase can be extended to 14 days. For those women who tolerate metformin poorly, the dose is subsequently increased to 500 mg twice daily with meals

for one week and then, the dose is increased to 850 mg twice time daily with meals and maintained at this level to three months[22]. Side-effects are mainly gastro-intestinal including diarrhea, nausea, vomiting or abdominal bloating. Side-effects can be minimized by administering with meals and increasing the dose gradually. Metformin should not be administered in a dose above 1.5 g per day. In patients with impaired renal function, lactic acidosis can occur. A systematic review of the use of metformin for ovulation induction for PCOS showed that up to 60% of women ovulate over 3-6 month period[23]. Metformin is an effective treatment of anovulation in women with PCOS, either as a first agent, but it is more effective in combination with clomiphene citrate[24].

Aromatase inhibitors

Aromatase inhibitors have been suggested as an alternative treatment to CC as the discrepancy between ovulation and pregnancy rates with CC has been attributed to its anti-estrogenic action and estrogen receptor depletion. The aromatase inhibitors do not possess the adverse anti-estrogenic effects of CC but, by suppressing estrogen production, mimic the central reduction of negative feedback through which CC works. Letrozole, the most prevalently used aromatase inhibitors for this indication, has been shown to be effective, in early trials, in inducing ovulation and pregnancy in women with anovulatory PCOS and inadequate CC response[25].

Gonadotrophin therapy

The main complications of gonadotrophin therapy, ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies, are both caused by multiple follicular development. Therefore, ovulation induction using gonadotrophins should be restricted to centers with the expertise and the equipment necessary to make appropriate clinical decision relating to the treatment and management of the associated complications.

Conventional protocol This protocol involves initial daily doses of 75-150 IU FSH treatment with increases of 75 IU FSH every 5-7 days, when needed. While ovulation rates of 70% were achieved, multiple pregnancy rates were observed to occur in 36% of pregnancies, and potentially life-threatening OHSS in 14%[26]. The conventional protocol, which is associated with unacceptably high multiple follicle development, multiple pregnancy and a significant incidence of OHSS, should not be employed to induce ovulation in patients with PCOS.

Chronic low-dose protocols Chronic low-dose protocols include: low-dose step-up protocol, low-dose step-down protocol and sequential step-up and step-down protocol.

Low-dose step-up protocol is the most commonly employed chronic low-dose regimen. This protocol involves initial daily doses of 75 IU FSH treatment for up to 14 days unless follicle maturity is reached. Ovarian response is initially monitored by serum estradiol concentrations every 2-3 days. When serum estradiol concentration exceeds 100 pg/ml, monitoring is continued by daily transvaginal ultrasonography and serum estradiol concentrations. If no ovarian response is noted after 14 days of 75 IU/day therapy, the daily FSH dose is increased by 37.5 IU. Any further FSH increment thereafter is made by 37.5 IU at weekly intervals to a maximum of 225 IU/day. If a dominant follicle emerges, the dose of FSH (threshold dose) is maintained until the follicle reaches a mean diameter of 17 mm. At that point, hCG at a dose of 10,000 IU is administered. If there are more than three follicles of 15 mm or greater in diameter, the cycle is cancelled due to the risk of multiple pregnancy and/or OHSS[27]. Recently, starting doses of 37.5 IU of rFSH were used with increments of 37.5 IU respectively when necessary. This protocol may be adequate to induce follicular growth[28]. The prediction of the threshold FSH dose is essential for optimization of ovulation induction using the low-dose step-up protocol. Body mass index (BMI) is an important prognostic factor that not only influences cycle cancellation due to no ovarian response[29] but also threshold FSH dose[30]. Chances for multiple follicular development during FSH induction of ovulation may be predicted by an initial serum androstenedione, ovarian response during preceding clomiphene citrate treatment and number of antral follicles on initial screening[31]. Conventional and low-dose step-up protocols yield comparable pregnancy rates. However, the major advantage of the low-dose step-up protocol is the achievement of high rate of monofollicular development about 70%[32].

Low-dose step-down protocol involves reducing (instead of increasing) the dose of gonadotrophins during the period of follicular development. Daily doses of 150 IU FSH is started and continued until a dominant follicle ($\geq$ 10 mm) is seen on transvaginal ultrasonography. The dose is then decreased to 112.5 IU per day followed by a further decrease to 75 IU per day 3 days later, which is continued until hCG is administered to induce ovulation[33]. However,

the step-up protocol using rFSH was recent reported to be significantly more efficient in obtaining monofollicular development and ovulation than the step-down protocol[34].

Sequential step-up and step-down protocol uses the principle that the FSH dependence of the leading follicle decreases as the follicle grows. In this protocol, a step-up approach is utilized, and the FSH dose is reduced by 37.5 IU FSH when the leading follicle reaches a diameter of 14 mm[35].

It may be concluded that gonadotrophin treatment is highly effective to achieve singleton live birth in infertile patients with PCOS, even in the current era of assisted reproduction[36].

Alternative and adjunct therapies Beyond the use of various low-dose regimens of gonadotrophin therapy, other strategies have been developed with the aim to improve the reproductive outcome in these women in terms of achieving successful pregnancy and reducing the risk for OHSS, multiple gestation, and miscarriages. These include the use of pulsatile gonadotrophin releasing hormone (GnRH) therapy and the use of pre-stimulation protocols using combined oral contraceptive pills and/or a GnRH analog therapy. Some evidence suggested that the use of pulsatile GnRH therapy may reduce the incidence of OHSS and multiple gestations. However, it does not appear to increase pregnancy rates and the reported abortion rates are high[37]. Pre-treatment with GnRH analog (GnRHa) therapy does not seem to prevent OHSS and/or improve pregnancy rates[38] but it may decrease the high spontaneous abortion rate in these women. Only one trial employing a GnRH antagonist with recombinant FSH, specifically for women with PCOS, has been reported. Following pre-treatment with oral contraceptives, a GnRH antagonist was started on day 2 of the cycle. When LH concen-trations 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 on-going pregnancy rates 28%[39].

Some other drugs have been used as adjuncts to gonadotrophin therapy which include dexamethasone for adrenal androgen suppression, dopamine agonists (when hyperprolactinemia is also present), growth hormone (GH) (hypothesized to improve ovarian responsiveness) and metformin (as an insulin-sensitizing agent).

Surgical ovulation induction

Laparoscopic ovarian drilling

Laparoscopic ovarian drilling [LOD] by diathermy or laser is a further treatment option for women with anovulatory infertility associated with PCOS. This treatment employs a unipolar coagulating current or puncture of the ovarian surface with a laser in 4-10 places to a depth of 4-10 mm on each ovary. About 82% of patients ovulated following the operation and 63% conceived either spontaneously or after treatment with medications to which they had previously been resistant[40]. A Cochrane data base analysis of six randomized controlled trials mostly comparing laparoscopic ovarian drilling with gonadotrophin therapy, showed similar cumulative ongoing pregnancy rates 6-12 months after LOD and after 3-6 cycles of gonadotrophin therapy[41]. The main advantage of LOD is a very high prevalence of monofollicular ovulation and therefore a significant reduction in multiple pregnancy rates compared with gonadotrophin therapy. However, the mechanism involved in the restoration of ovulation is quite unknown although the principle endocrine change is a dramatic decrease in LH concentrations about two days after the operation. Those who are slim and have high LH concentrations seem to have the most favorable prognosis[42].

In vitro fertilization and embryo transfer (IVF/ET)

In-vitro fertilization is a last option providing excellent results. The outcome of assisted reproduction in the PCOS patient is similar to matched controls treated for other indications. Furthermore, the presence of polycystic ovaries may confer an advantage regarding the number of oocytes retrieved and the number of embryos available for transfer and cryopreservation. However, ovarian stimulation is especially difficult in these patients due to a serious risk of severe hyperstimulation. Therefore, in the PCOS patient undergoing ovarian stimulation the following are recommended: (1) The use of GnRHa in a long protocol to effectively suppress LH concentration, (2) The use of step-down gonadotrophin regimens to stimulate the ovaries, (3) Coasting when estradiol concentrations are very high, (4) Insulin sensitizing medications in the hyperinsulinemic insulin-resistant patient.

In vitro maturation (IVM) of oocytes retrieved from non-stimulated or minimally stimulated cycles from women with PCOS may become a possible option that should be considered seriously when assisted conception is attempted. However, it is proving techni-

cally difficult at present and concerns over the well being of pregnancies achieved from IVM have not yet been fully answered. Results of IVM should be improved further and generalized before the technique can be advocated as the initial treatment approach in these patients[44].

In conclusion, diet and exercise are the initial treatments, followed by ovulation induction with clomiphene and/or metformin. Resistant patients can then be treated with either ovarian cautery or gonadotrophins. When stimulating women with PCO for IVF, the increased risk of OHSS has to be considered.

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