

Infertility Treatment in Patients with Polycystic Ovary Syndrome (PCOS)

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Introduction

The polycystic ovary syndrome (PCOS) is the most common endocrine disorders that affect between 10-15% of women during their reproductive ages [1]. Depending on the criteria used for diagnosis of polycystic ovary syndrome, the prevalence ranges up to 30% [2,3]. Most of those women have only ultrasound appearance of polycystic ovaries but without additional hormonal or menstrual disturbances that characterizes classic PCOS. To prevent heterogeneity in the diagnosis and reporting of PCOS, the most commonly used diagnostic criteria today, are those from Rotterdam consensus, published in 2003 and revised in 2004 [4]. Diagnostic criteria for PCOS are based on at least 2 of the following 3 criteria: a) oligo-ovulation and/or an ovulation, b) clinical and/or biochemical evidence of androgen excess and c) ultrasound assessment of >12 small antral follicles in each ovary or ovarian volume >10cm³. The other commonly used criteria are those from US National Institutes of Health, released in 1990. The NIH definition requires both criteria to make the diagnosis: a) chronic anovulation and b) clinical and/or biochemical evidence of androgen excess [5].

The etiology of PCOS remains unknown, although there is increasing evidence to support the view that PCOS is a complex endocrine trait involving the contribution of several genes and that these genes act jointly with environmental, particularly nutritional, factors [6].

Hereditary component of the disorder lies on genetic basis which may include more than one gene (CYP17, CYP11a, VNTR etc.) [7,8].

Abnormal ovarian steroidogenesis is well known fact that depicts its origin in the ovarian hyperandrogen production, but it is also influenced by the extraovarian factors such as over-secretion of LH and of insulin.

Metabolic disorders such as elevated levels of LH [9], prolactin [10], insulin and androgens are common and can have long-term health consequences of PCOS women. LH hypersecretion is associated with menstrual disorders and subsequent infertility. Hypersecretion of LH occurs in approximately 40% women with PCOS and effects the ovarian androgenic production, but may also have negative effect on ovulation and abortion rates by direct interference with oocyte maturation [11]. It also linked with reduced implantation and pregnancy rate in both, natural and assisted pregnancies (ART). The level of estradiol during the early follicular phase of the menstrual cycle is equal to those in healthy women. The level of estrone is however, elevated, largely due to extra-ovarian conversion of androstenedione [12], which mostly takes place in adipose tissue. The association between overweight (BMI 25-30 kg/m²) and obesity (BMI >30 kg/m²) with PCOS is well-known, but the reason has not yet been established. The prevalence of obesity varied widely across different geographic areas, from 25% in China to 85% in USA, Australia and Poland [13-15]. When waist circumference and waist-to-hip ratio of women with PCOS increases their reproductive function and metabolic state is altered more than in cases without such changes [14].

Infertility Treatment Options

Hyperandrogenism and menstrual disorders are the most common

problems in young PCOS patients, while elevated levels of androgens, oligomenorrhea or amenorrhea, and particularly infertility are the most common problems of PCOS women in reproductive age.

The anovulation is the leading cause of infertility in this syndrome with prevalence of 68% [16]. Recent findings indicate disturbances of the earliest i.e. gonadotropin-independent stages of follicular development PCOS [17,18] that may contribute to the mechanism of anovulation.

Several methods have proved to be effective treatment of infertility in women with PCOS [19,20]:

Conservative

Life-style modifications such as weight loss and exercise (first-line of treatment): Losing weight through exercise and diet has been proven effective in restoring ovulatory cycles and achieving pregnancy for many of over-weight and obese PCOS patients. Weight loss of only 5% to 10% of total body weight often leads to the return of ovulatory cycles. Life-style modifications are highly important for ovulation induction since the findings suggest that obese women are less likely to show good response without weight reduction and exercise.

Clomiphene citrate (CC) for ovulation induction (first-line of treatment): Ovulation induction can be accomplished in 60-80% of women with PCOS by the use of anti-estrogen, typically clomiphene citrate. The starting dose of CC is 50 mg/per day for 5 days, starting between day 2 and 5 of current menstrual cycle. In the case of unsuccessful ovulatory response, the dose should be increased but not over 100mg per day. Cycle monitoring should be taken into account at least during the first cycle of treatment and when doses must be increased because of the ovulation failure. Successful ovulatory response usually means serum levels of progesterone >10nmol/L tested 6-8 days before the onset of menstruation, detection of pre-ovulatory LH surge with urinary kits and vaginal ultrasound assessment of follicular development and endometrial thickness.

Aromatase inhibitors for ovulation induction (second-line of treatment): Aromatase inhibitors such as letrozole (Femara®) block the conversion of testosterone and androstenedione to estradiol and estrone. In this way letrozole prevents the negative feedback at the hypothalamic-pituitary axis and leads to increased secretion of gonadotropins, which in turn leads to ovarian follicular growth and development. Expected pregnancy and abortion rate is similar to CC (around 15%), although aromatase inhibitors have less detrimental effect upon endometrium. Reasonable concern rose after results of the Biljan et al. [21] study which reported an increased risk of cardiac and skeletal abnormalities in infants born after the use of letrozole in ovulation induction. American

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and Canadian obstetric and gynecological societies have immediately posted a warning letter. But recent research, above all by Tulandi and colleagues [22] on 911 infants, found no increased risk of congenital abnormalities and anomalies in infants of mothers who used letrozole in ovulation induction (i.e. incidence was 2.4% for the letrozole and 4.8% for the CC group).

Insulin sensitizing agents (Metformin) alone or in combination with CC (second-line of treatment): Risk of impaired glucose tolerance (IGT) and diabetes is highest in women who have both, menstrual disorder (oligo-ovulation or anovulation) and hyperandrogenism, and the risk is further amplified by the obesity. Metformin treatment is indicated in those with IGT or in the case of frank diabetes. Metformin in combination with CC may increase the rate of ovulation and pregnancy, but does not significantly improve the rate of live births over that of the CC alone. Metformin can be also added to CC in women who show resistance to clomiphene, who are older and/or have visceral obesity. Starting dose is typically 250-500mg per day and increases to optimal dosage of 500mg, 3 times daily. Side-effect usually accounts for nausea, bloating and diarrhea.

Gonadotropins (second-line of treatment): Gonadotropins are treatment of choice in PCOS women who fail to ovulate or to conceive with oral ovulation induction drugs. Ovarian response should be monitored by the serial ultrasound measurement of follicular growth and endometrial development (endometrial thickness and lining). Laboratory assessments are equally important and consist of serial serum estradiol measurement, supported with LH and/or progesterone when needed. Pregnancy rates with gonadotropins (mostly used drug is recombinant FSH) are 20-25% per cycle, but with drawbacks of intensive cycle monitoring, treatment cost, multiple pregnancies and risk of ovarian hyperstimulation syndrome (OHSS).

In vitro fertilization (IVF) (third-line treatment): Studies have shown that the use of gonadotropin-releasing hormone (GnRH) agonist leads to higher rates of successful pregnancy and lower rates of abortion when compared with CC treatment [23].

Pregnancy rates can approach 40% per cycle with IVF. Nevertheless IVF remains in most cases reserved for clomiphene resistant patients, and those that have other causes of infertility other than anovulation (mechanical or male factor). The reason for this contradiction lies in the fact that therapy with GnRH analogues is complicated, longer, and expansive, requires the use of higher doses of gonadotropins to achieve ovulation, increases the number of follicles obtained, and thus the chance for multiple births [24].

Surgical

Ovarian drilling (second-line treatment; indicated cases): Laparoscopic ovarian drilling may be as effective as low-dose FSH in inducing the ovulation, but additional therapy with CC and/or FSH is also required after surgery in 2/3 of cases [25]. Laparoscopic ovarian drilling may be considered in women with clomiphene-resistant PCOS, particularly when there are other indications for laparoscopy, but surgical risks from procedure itself and postoperative adhesion formations remains a concern.

Conclusions

First line of infertility treatment should be started with weight loss of 5-10% and changes in life-style (regular exercise, reduction or abstinence of smoking, coffee and alcohol intake) that will restore ovulation in majority of overweight and obese PCOS patients. Clomiphene citrate remains the first-line treatment as affordable,

patient-friendly and highly successful in ovulation induction (~60-80% of PCOS patients) despite negative anti-estrogenic effect on the endometrium and higher abortion rates than gonadotropin intramuscular injections.

Second line of infertility treatment in PCOS patient is insulin sensitizing drugs and aromatase inhibitors. Insulin sensitizing agents such as Metformin by improving the body's response to insulin will also lower the ovarian hyperandrogenism, which increases the likelihood of ovulation. Combination of CC and Metformin will slightly but not significantly increase the chance of successful ovulation than the use of CC alone (~5%). Metformin may be beneficial in older PCOS women and those who have predominant abdominal obesity or fail to ovulate on CC alone. Aromatase inhibitors, in particular Letrozole have been equally effective as CC in induction of ovulation with similar pregnancy rate (~15%) but without anti-estrogens effect upon endometrium. Further clinical studies are needed to confirm their effectiveness, optimal dosage and safety in the routine use of ovulation induction.

The next step in second line of treatment is the intramuscular gonadotropins. Gonadotropins directly increase the amount of FSH circulating in the body, promoting the growth and development of mature follicles. Careful cycle monitoring of follicular and endometrial development through ultrasound and blood tests are needed in order to trigger the ovulation with human chorionic gonadotropin (HCG). This will allow more precise timing (around 36 hours after HCG injection the ovulation occurs) of intercourse or intrauterine insemination (IUI).

Finally, if the patient does not become pregnant within 6-12 months of ovulation induction treatments mentioned previously the use of third line treatment should be reserved for IVF, a complex and expensive process of a controlled ovarian hyperstimulation with GnRH analogues, gonadotropins and careful ultrasound and laboratory assessments that proved to be highly effective.

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