Chapter 6

Ovulation Induction in Women with Polycystic Ovary Syndrome: What is the Optimal Option?

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Additional information is available at the end of the chapter

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Abstract

Infertility is a distressing medical and psychosocial problem afflicting about a quarter of all couples wanting to reproduce their offspring. Majority of the anovulatory problem in the female, as a cause of infertility, is due to polycystic ovary syndrome (PCOS). This condition is a complex interplay of factors, which affect women even beyond their fertility. It has been found to increase the risk of other adverse conditions such as the metabolic syndrome, cardiovascular diseases, type II diabetes mellitus, and endometrial cancer as well as infertility. Different groups have made diagnosis of PCOS with various diagnostic criteria. The Rotterdam criteria used in the diagnosis of PCOS mainly emphasize the reproductive malfunctions of this complex disease. The treatment of anovulatory infertility in PCOS is as enigmatic as the disease itself. Various methods have been deployed to treat the anovulation with variable success. Clomiphene citrate is a traditional first-line drug in treating anovulation in women with PCOS. Weight reduction, letrozole, metformin, follicle-stimulating hormone (FSH) and ovarian drilling are some of the other ways in which anovulation has been treated in these women. What method is more likely to succeed in treating the infertility from anovulation in PCOS and in what circumstance are the subject matters of this discussion.

Keywords: polycystic ovary syndrome, ovulation induction in PCOS, anovulatory infertility, clomiphene citrate, letrozole

1. Introduction

Polycystic ovarian syndrome (PCOS) is a group of heterogeneous endocrine disease affecting women characterized by irregular menses, hyperandrogenism, and polycystic ovaries. The diagnoses of polycystic ovarian syndrome are frequently made for the first time in the infertility clinic during evaluations for infertility. Infertility is the main clinical manifestation of

ovulatory dysfunction in patients with PCOS. The prevalence is between 8.5 and 20% depending on the criteria used for the identification of the condition [1, 2].

Anovulation is a cause of infertility in up to a quarter of all cases of infertility. Normogonadotropic anovulation classified as World Health Organization (WHO) group II is the most common category of anovulatory infertility. PCOS is the most common in this group and notably the commonest endocrine disorder and cause of anovulation [1–3]. Insulin resistance is implicated in the ovulatory dysfunction in PCOS by disrupting the hypothalamo-pituitary-ovarian axis. Insulin resistance also leads to other comorbidities such as metabolic syndrome, hypertension, dyslipidemia, glucose intolerance, and diabetes mellitus as well as mental disorders such as depression, anxiety, bipolar disorders and binge eating [1, 4]. Women with PCOS present to the fertility clinic with chronic oligo/anovulation and hyperandrogenism, with attendant negative effects on their fertility. The desire to reproduce is very intense in many communities where there is high premium placed on reproduction as a means of survival. So, these women having learnt the diagnosis of their conditions are very expectant that their conditions will soon be reversed following treatment such that they could ovulate, become pregnant, and successfully have children. Many a times, the drug to bring about the reversal of anovulation refuses to work due to innate characteristics within the woman, the drug, or even the environment. This challenge has led to the development and use of several different pharmacologic agents used singularly and in combination to deal with the challenge of anovulation. Other physical methods and herbal preparations have also been deployed to varying degree of success to combat anovulation in women with PCOS.

Central to the management of women with infertility from PCOS is the induction of ovulation. The treatment options for infertility in women with PCOS include clomiphene citrate, gonadotropins, laparoscopic ovarian drilling (LOD), and assisted reproductive technology [1, 5]. Common to all methods is the induction of ovulation. Letrozole and metformin also play important roles in ovulation induction as has been now well demonstrated. The use of these pharmacologic agents has been shown to be superior to placebo or no treatment in terms of pregnancy or ovulation [6].

2. Weight reduction and ovulation induction

Scientific studies have not confirmed that women could regain spontaneous ovulation with voluntary weight loss and other life style modifications as systematic reviews did not identify studies that confirm that ovulation and other clinical reproductive outcomes improved with weight loss in women with PCOS but the studies identified increased total testosterone, androgen index, hirsute, fasting blood glucose, fasting insulin, and worsened lipid profile in the obese women compared with normal weight women with PCOS [7–9]. Obesity is linked to anolution and pregnancy loss as well as poor response with ovulation induction methods such as clomiphene citrate, gonadotropins, letrozole, and ovarian drilling [10–15]. This is important as previous authors have surmised that since obesity is found in some women with PCOS and worsens insulin resistance, that weight loss would improve ovulation and other reproductive outcomes [4, 16–19].

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The American societies studying PCOS indicate that weight loss is a primary therapy in PCOS. That weight loss as little as 5–10% of body weight can regularize menses and improve response to ovulation induction and fertility medications [9, 12].

In many countries, lifestyle intervention is recommended as this has led to higher spontaneous ovulation rates and natural conception rates [20, 21].

Weight reduction through dietary modification and exercise is recommended for overweight PCOS patient [22]. Some studies show that over 10% of women with PCOS will regain spontaneous ovulation when placed on low calorie, low-fat diet, and exercise or with surgery. The aim of dietary restriction and exercise is toward losing about 5–10% of their body weight. This form of treatment alone or in combination with pharmacologic agents would reduce insulin resistance and is advocated for overweight to obese women of BMI > 24 [22]. The drawbacks of this method of treatment are that such women lack the motivation to remain on diet and exercise, and may not be able to achieve the desired weight loss to trigger spontaneous ovulation, and most times pharmacologic agents are added to assist ovulation. The duration it takes to achieve the desired body weight to bring about ovulation is not defined, but differs among patients. Other drawbacks are that it may not treat anovulation in normal-weight women even though they also have insulin resistance as well. The advantage is that it is cost-effective and will not produce any form of drug reactions. It will also reduce the high level of luteinizing hormone and reduce early pregnancy loss. A combination of lifestyle modification with weight loss before pharmacologic ovulation-inducing agents improved ovulation and live birth in women with PCOS in a USA study [23] and in addition, required lower doses of pharmacologic agent for ovulation induction.

3. Pharmacologic agents and ovulation induction

3.1. Use of pharmacologic agents in induction of ovulation

Several pharmacologic agents have been used to induce ovulation in these patients. They have achieved varied success with attendant setbacks from these drugs especially in achieving pregnancy and with adverse pregnancy outcomes. These drugs include clomiphene citrate, metformin, letrozole, gonadotropins, inositol, and tamoxifen.

3.1.1. Clomiphene citrate

Clomiphene citrate is traditionally the first-line drug used to induce ovulation in women with anovulation due to PCOS [2]. This drug has both estrogenic agonist and antagonist effects. It produces its effect principally by blocking the estrogen receptors in the hypothalamus to increase the endogenous follicle-stimulating hormone (FSH) to bring about folliculogenesis and ovulation. Clomiphene citrate when compared to other pharmacologic agents used for induction have been found to be inferior to drugs like letrozole, or a combination of clomiphene citrate and metformin with respect to ovulation, pregnancy, or live birth [6]. Clomiphene citrate in combination with metformin showed a higher pregnancy rate than clomiphene citrate alone or metformin alone. The odds ratio for pregnancy when clomiphene citrate in combination with metformin is compared to clomiphene citrate alone is 1.8 (1.35–2.42) indicating that clomiphene

citrate in combination with metformin is a better treatment and offers 1.8 times the chance of pregnancy compared to the clomiphene citrate alone.

A small group patients do not ovulate at a maximum dose of 150 mg of clomiphene citrate for 5 days; they are taken to be clomiphene-resistant and anyone unable to achieve pregnancy for a period of 6 months on clomiphene citrate is termed to have clomiphene failure. Those resistant to clomiphene citrate will require other forms of ovulation induction, which may include a combination of the clomiphene citrate and metformin, other pharmacologic therapy or ovarian drilling to produce ovulation in this subset of women. Other disadvantages of clomiphene citrate are its antagonist effect on the estrogen receptors within the endometrium, which is thought to reduce the pregnancy rates in women treated with clomiphene citrate. The rates of multiple pregnancies with clomiphene citrate are below 10% and the risk of ovarian hyperstimulation is rare when compared to follicle stimulating hormone with higher chances of both multiple pregnancy and ovarian hyperstimulation syndrome [23]. The prolonged use of clomiphene may increase the risk development of uterine fibroid or endometrial cancer.

3.1.2. Letrozole

Letrozole is a third-generation aromatase inhibitor. In inducing ovulation, the drug acts primarily in the ovary where it antagonizes the effect of the enzyme 5α-reductase in the production of estrogen in the ovary. Its effect is to inhibit the conversion of testosterone and androstienedione to estradiol and estrone. It also blocks the conversion of androgen to estrogens in the peripheral fat cells and suppresses local estrogen production in the brain. The reduced levels of estrogen release the hypothalamus from the negative feedback effects of estrogen and cause increased production of FSH for folliculogenesis and ovulation.

Letrozole has been found to be superior to clomiphene citrate alone or even clomiphene citrate in combination with metformin. The systemic review and meta-analysis of the Rui Wang group showed that Letrozole produced a higher pregnancy and ovulation rates when compared with clomiphene citrate alone. The odds ratio for pregnancy or ovulation with letrozole compared with clomiphene citrate is 1.58 and 1.99, respectively. Similar outcome was also noted when compared to tamoxifen (another estrogen antagonist similar to clomiphene citrate).

Letrozole also led to higher live-birth rates when compared to clomiphene citrate alone. The chances of birth with letrozole are about 1.6 times higher than clomiphene. It also resulted in lower multiple pregnancy rates compared to the clomiphene citrate. In these regards, Letrozole is better than the clomiphene citrate used traditionally to induce ovulation in women with PCOS. However, the systematic review acceptably did not review the negative effects of these drugs. It also found that the risks of abortions are lower with letrozole group [6]. In patients with clomiphene citrate resistance, Letrozole in combination with metformin showed better efficacy than clomiphene-metformin combination in terms of ovulation rates, pregnancy rates, and live births rates. It also has less abortion rates in the meta-analysis of treatments of patients with clomiphene citrate-resistant PCOS [24].

Letrozole can be used as a first-line drug in the treatment of anovulation because of its higher ovulation, pregnancy and live birth rates, and lower multiple pregnancy rates. The main advantage of letrozole over clomiphene citrate or clomiphene citrate combination with

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metformin is the absence of anti-estrogenic effects at the level of the endometrium, which perhaps is responsible for its higher pregnancy and live birth rates [1]. Despite the promising results with letrozole, neither letrozole nor metformin is approved for the treatment of anovulation in many countries and it is outrightly prohibited in several other countries.

3.1.3. Metformin

Metformin is an oral hypoglycemic agent; a biguanide used for treatment of type 2 diabetes mellitus. It works as insulin sensitizer and reduces insulin resistance, which is a feature in PCOS. It improves ovulation and other reproductive functions. It assists in weight reduction and its effect is better in obese women with PCOS. Alone, metformin is a weak induction agent. However, it is very effective when used along with clomiphene citrate for the induction of ovulation in the patients with PCOS. When metformin is given in combination with clomiphene citrate, there were significantly higher pregnancy rates than metformin or clomiphene citrate alone. The chances of pregnancy increased over 1.7 times in those with the combination of clomiphene and metformin when compared to metformin alone. Letrozole and metformin are also superior to metformin or letrozole alone in inducing ovulation. However, metformin is also useful after ovarian drilling. It reduces insulin resistance and androgens levels, and increases ovulation and pregnancy rates in clomiphene citrate-resistant PCOS after laparoscopic ovarian drilling (LOD).

3.1.4. Gonadotropins

The gonadotropins have been used to bring about ovulation in several anovulatory conditions including PCOS. It acts directly on the primordial follicles replacing endogenous gonadotropins to bring about folliculogenesis and ovulation. All forms of gonadotropins ranging from the human menopausal gonadotropins (HMG) to the highly purified follicle stimulating hormone have been recognized to cause ovulation in women. The active agent is the follicle stimulating hormone. The major set back has been that it cannot be administered orally. When compared to other pharmacologic agents, the efficacy of the follicle-stimulating hormone in bringing about ovulation is the highest. It also has the highest live birth rates after letrozole in the network meta-analysis comparing the efficacy in the use of these agents [6]. In the patient with clomiphene resistance, FSH was superior to clomiphene-metformin combination in ovulation rates, pregnancy, and live birth rates as well [1]. The follicle-stimulating hormone led to a higher multiple pregnancy rates when compared to the other pharmacologic agents with a higher risk of ovarian hyperstimulation syndrome. These are the two most serious side effects of gonadotropins resulting from simultaneous growth of many follicles [6, 18, 25]. Gonadotropins could be the second-line drug for clomiphene-resistant PCOS patients [26, 27].

4. Surgery and ovulation induction

4.1. Use of ovarian drilling to induce ovulation

Laparoscopic ovarian drilling has been demonstrated to induce ovulation in women with PCOS. This method of ovulation induction is used for clomiphene-resistant and FSH-resistant PCOS.

The mechanism involved in the ovarian diathermy is that it leads to the correction of hypersecretion of LH brought about by modification of the ovarian pituitary feedback. The practice is to drill into both ovaries. However, unilateral drilling has been found to bring about ovulation in either ovaries as well [1, 15, 26]. A net meta-analysis comparing its use as an ovulation induction agent did not find it superior to placebo or no treatment. It had no significantly higher chance at pregnancy or higher pregnancy rates in women with PCOS [6]. In patients with clomiphene resistance where it is being advocated, LOD was found to reduce testosterone and Luteinising hormone levels and associated with more regular cycles, higher ovulation and pregnancy rates compared to metformin alone even though metformin results in more attenuation of luteinizing hormone [28]. Emerging evidence shows that unilateral ovarian drilling has similar effects as bilateral ovarian drilling in bringing about ovulation, pregnancy rates, and life birth rates. Reported pregnancy rates are lower than in treatment with HMG [24]. The seeming comparative advantage of LOD is in its one-off therapy, especially in patients with clomiphene citrate resistance, sustained reversal of the pathology, high ovulation and pregnancy rates, reduced risk of multiple pregnancy, and ovarian hyperstimulation syndrome as well as patient's acceptability [26]. LOD with elecrocautery was found to be superior in treating anovulation compared to laser drilling or use of gonadotropins in clomiphene-resistant PCOS patients. The major side effects of LOD are the fact that it is a theater procedure and requires anesthesia; it may reduce ovarian reserve and has been associated with peri-ovarian adhesions [29, 30]. When ranked according to efficacy of ovulation induction, the systemic review found out that the clomiphene citrate in combination with metformin was the most efficacious followed by follicle-stimulating hormone, letrozole, metformin, clomiphene, tamoxifen, laparoscopic ovarian drilling, and placebo or no treatment in that order. This when ranked in percentage efficacy of effectiveness showed 90, 82, 80, 50, 46, 27, 22 and 3%, respectively [6].

4.2. Use of bariatric surgery to induce ovulation

Bariatric surgery has been used for weight reduction among highly obese women who had bariatric surgery for just weight reduction. The bariatric surgery in obese PCOS patient also resulted in weight loss, spontaneous ovulation, and pregnancy.

5. Conclusion

However, when the ranking in terms of live birth rate was done, letrozole (81%) gave the best result, followed by follicle-stimulating hormone (74%), clomiphene-metformin (71%), tamoxifen (48%), clomiphene citrate (36%), metformin (30%), placebo or no treatment (10%).

Women with PCOS should undergo pre-conception counseling before any treatment for infertility. The importance of life-style modification, especially weight loss and exercise, should be emphasized and encouraged in overweight women, and smoking and alcohol consumption should be discouraged [24]. More randomized trial to determine the effect of weight loss to ovulation should be undertaken to elucidate clearly the place of weight loss as a means of ovulation of induction considering its affordability and acceptability as a means of treatment.

The controversy with the method of treating anovulatory infertility in women with PCOS will continue for some time. The systemic review found out that the clomiphene citrate in combination with metformin was the most efficacious followed by follicle-stimulating hormone, letrozole, metformin, clomiphene, tamoxifen, laparoscopic ovarian drilling, and placebo or no treatment in that order. However, when the ranking in terms of live birth rate was done, letrozole, follicle-stimulating hormone, clomiphene-metformin, tamoxifen, clomiphene citrate, metformin, placebo or no treatment was noted. It will therefore seem reasonable to include letrozole, clomiphene citrate and the combination of clomiphene citrate with metformin as possible first-line drugs in the treatment of anovulatory infertility in women with PCOS. While the gonadotropins is reserved as a second-line drug for these women, ovarian drilling is recommended after failure with the gonadotropins or whenever laparoscopy is indicated for any other reason in these women with failed clomiphene resistance. It will be advisable to refer patients that fail to achieve pregnancy using the methods above for assisted reproductive therapy for the treatment of their anovulatory infertility.

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