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REVIEW ARTICLE

TREATMENT OUTCOMES IN PCOS (POLYCYSTIC OVARIAN SYNDROME)-RELATED INFERTILITY

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Abstract

Polycystic ovarian syndrome (PCOS) is one of the underdiagnosed endocrine disorders found to be prevalent among females in the reproductive age group. PCOS effects on an average 8-13% of reproductive aged women, globally. This condition is responsible for causing distress physiologically and psychologically paving the way for a poor quality of life. One of the devastating complications of PCOS is infertility. At present, there is no treatment for PCOS but could be managed by alternate options such as lifestyle modification to *in-vitro* fertilization. The primary objective of this review article is to analyze the outcomes of certain pharmacological treatment options such as clomiphene citrate which is a selective estrogen receptor modulator, Letrozole an aromatase inhibitor, and gonadotropins for PCOS-related infertility. Clomiphene citrate binds to estrogen receptors indirectly increasing the gonadotropins. Studies confirm a 35-40% successful outcome. Letrozole similarly increases gonadotropins by indirectly decreasing estrogen. A notable increase in the successful outcome was observed with both clomiphene citrate and letrozole, with almost near similar results. The pregnancy outcome was approximately 40% with clomiphene citrate, while letrozole showed 50%. Notably, more side effects were observed in the administration of clomiphene citrate compared to letrozole. Human menopausal gonadotropin (hMG) and recombinant follicle-stimulating hormone (FSHr), that are gonadotropins, were used as they are directly responsible for the maturation of follicles and ovulation itself. The use of gonadotropins increased the pregnancy rate outcome to 20 -30%, albeit with the risk of multiple births. Furthermore, we have discussed why letrozole and clomiphene citrate are used as the primary therapy compared to gonadotropins.

Keywords: Clomiphene citrate, gonadotropins, infertility, letrozole, Polycystic ovarian syndrome (PCOS).

INTRODUCTION

Among the several endocrine disorders, PCOS is found to be the most common disorder affecting the females of reproductive age, globally. Up to 8-13% of women in the post pubertal age group are affected. Unfortunately, as many as 70% of cases remain undiagnosed. It affects women both biologically and psychologically, causing significant distress and poor quality of life[1]. PCOS is a characterized by amenorrhea, obesity signs of hyperandrogenism such as hirsutism and acne associated with enlarged polycystic ovaries. Furthermore, infertility is exceedingly prevalent among these patients as well[2].

The heterogeneous nature makes it a challenging diagnosis to make, which explains why a significant number of cases remain undiagnosed. Currently, the most widely used method of diagnosis is using the Rotterdam criteria as it was found to be the most inclusive. For diagnosis of PCOS, the Rotterdam criteria are used. Two out of the three following symptoms is to be present: 1. Oligo/anovulation, 2. Hyperandrogenism and 3. Polycystic ovaries[3].

Adding to the numerous symptoms of PCOS, these patients are at risk for devastating complications as well. They are at greater risk of developing Type II diabetes mellitus due to insulin resistance. Hyperinsulinemia increases the risk of dyslipidemia and cardiovascular diseases. The long-term, tonic hyperestrogenic state leads to endometrial hyperplasia, which in turn causes abnormal uterine bleeding, and may even lead to endometrial cancer[2].

An ovulatory infertility is most commonly caused by PCOS[4]. Women affected by PCOS require a healthy,

safe pregnancy may need treatments to optimize their condition in order to improve their metabolic state and fertility. These patients have the option of lifestyle modifications, ovulation induction, insulin sensitizers, and even surgical methods in order to overcome this disorder. This article will focus on the medical management of these patients, specifically ovulation induction, with comparisons between the various drugs that are currently employed[2].

Treatment options available for PCOS

There is no definite cure for PCOS as of now. Therefore, treatment focuses on a comprehensive and holistic approach to the many different manifestations of this disease. The main goals may differ from patient to patient depending on their needs such as fertility issues, insulin resistance and risk of developing type II diabetes, metabolic issues, etc. This includes reducing the features of hyperandrogenism, preventing the development of insulin resistance, treating metabolic abnormalities, as well as procreative management in order to address fertility issues and obtain a safe pregnancy. Overall, the treatment should be targeted toward improving the well-being and quality of life of these patients[5].

The main treatment modalities include lifestyle modifications, medical management, as well as some surgical options. The treatment is targeted towards specific issues that the patient is struggling with at the time. For example, a patient complaining of excessive weight gain may benefit from lifestyle modifications. A healthy diet and regular exercise along with smoking and alcohol cessation can show improvements for various manifestations of PCOS, without the need for medications. It can reduce weight, thereby reduces the risk of resistance to insulin and development of type II diabetes mellitus, help regulate the menstrual cycle, and stimulate regular ovulation as well[6].

In cases where the desired results are not achieved through lifestyle modifications, various medications are used. Oral contraceptive pills have been used to address the issues related to acne and excessive hair growth associated with hyperandrogenism, as well as to regulate the menstrual cycle. Metformin is used for insulin resistance. For obesity, Liraglutide, a glucagon-like peptide receptor 1 agonist or Orlistat, a lipase inhibitor is used to induce weight loss[5].

If the above-mentioned treatments do not aid in managing infertility, the secondary treatment is induction of ovulation if there are no indications for *in-vitro* fertilization such as male factor or tubal obstruction. Some of the treatment includes clomiphene citrate, letrozole, along with gonadotropins which will be discussed in detail[5]. Although uncommon, surgical methods such as laparoscopic ovarian drilling may be done in cases refractory to medical management[2].

Selective estrogen receptor modulator: Clomiphene citrate

Clomiphene citrate, whichis two equal quantities of optical isomers, zuclomiphene, and enclomiphene. It has been used for several decades to induce ovulation. Zuclomiphene, the more potent of the two, makes up to 38% of the total drug quantity[7], whereas the trans isomer, enclomiphene, has a shorter half-life[8].

Ovulation induction associated with clomiphene citrate is associated with the drug binding to estrogen receptors. As the hypothalamic estrogen receptors are depleted, the brain perceives the estrogen concentrations as low. This triggers the negative feedback, and there is increased secretion of gonadotropin-releasing hormone. This, in turn, increases ovarian follicular activity, which results in the inhibition of estrogen through negative feedback mechanism on the hypothalamus[9].

However, Clomiphene citrate is known to be associated with the risk of twins, triplets and quadruplets[10]. Other side effects, although common, are transient, such as headaches, hot flashes, blurred vision and mood changes. It is contraindicated in known hypersensitivity, pregnancy, liver disease, ovarian cysts, and abnormal uterine bleeding[8]. In one study, a group of patients treated with clomiphene citrate, ovulation was shown to occur in 80% of the patients, while 35-40% got pregnant. Among this group around 20-25% showed no response and was considered to be resistant[11]. A study that compared the 10 days of clomiphene citrate treatment regimen with the 5-day regimen, pregnancy rates and live birth were higher with 10-day treatment schedule[12].

Another selective estrogen receptor modulator used in PCOS-related infertility is tamoxifen. However, studies showed that there is no stark differences were observed in terms of ovulation and pregnancy rate, in patients treated with tamoxifen and clomiphene citrate[13]. It has been reported that zuclomiphene may be the cause for the unwanted effects of clomiphene citrate[8]. Although used for ovulation induction, clomiphene-induced endometrial thinning, poor cervical mucus production, and clomiphene resistance among the population, affect the effectiveness of the drug in terms of ovulation induction[14].

For several years' clomiphene citrate was the first line of treatment for ovulation induction[15]. However, letrozole is now the first line of treatment[16], as the rate of ovulation and live birth are higher in patients who received letrozole, in comparison to those who received clomiphene citrate[17].

Aromatase inhibitors: Letrozole

Aromatase inhibitors comprises of steroidal or nonsteroidal drugs[18]. Among which, currently there are three 3rd generation drugs that are used clinically. Letrozole and Anastrozole is under the category of nonsteroidal aromatase inhibitors and whereas, Exemestane is a steroidal aromatase inhibitor[18,19]. Among these, Letrozole is now being used widely for ovulation induction and is considered as the first-line of therapy for the treatment of infertility in patients suffering from PCOS[20].

Letrozole is obtainable as 2.5 mg tablets, and it can either used for the treatment of breast cancer in women who attained menopause, or it can be used as an agent to induce ovulation as stated above[19]. For ovulation induction, Letrozole is prescribed daily for 5 days, starting on the 3rd day of the menstrual cycle, with a dose ranging between 2.5 mg to 7.5 mg[21,22].

The mechanism of action of aromatase inhibitors, as the name suggests, is inhibition of the action of the enzyme aromatase. Aromatase catalyzes the demethylation of androgens, to produce estrogens, in the ovarian follicle, peripheral tissue and the brain[22]. Aromatase inhibitors act by inhibiting the conversion of testosterone and androstenedione to estradiol and estrone, respectively, and consequently suppresses the biosynthesis of estrogen[23]. As a result, the low estrogen levels activate a positive feedback mechanism in the hypothalamic-pituitary axis, increasing the release of gonadotropin-releasing hormones that in turn stimulates the production of follicle-stimulating hormone[22]. Increasing follicle-stimulating hormone promotes folliculogenesis and follicular maturation, with subsequent improvement in ovulatory rates[23].

Prior to administration of letrozole, caution must be taken, as there are contraindications to the drug. The two major contraindications for administration of aromatase inhibitors are listed below[24].

1. Pregnancy and premenopausal women: Prescribing letrozole in these patients can cause harm to the growing fetus to the extent that there is a risk of loss of pregnancy.
2. Hypersensitivity: If letrozole is prescribed to a patient who is hypersensitive to the drug, it can cause urticaria, angioedema, and anaphylactic reactions.

Patients who are already on letrozole experience certain side effects due to the drug, and these are usually similar to that of menopause such as hot flashes, sweating, insomnia, asthenia, low mood, etc. Other side effects are symptoms such as nausea, loss of appetite, hair loss, vaginal dryness, bleeding, mild arthralgia and myalgia[19-25]. In addition to this, the increased bone loss due to long-term estrogen deficiency can predispose patients taking letrozole to develop osteoporosis, bone pain, fractures, and other long-term side effects such as hypertension, hyperlipidemia, and hypercholesterolemia[19-25].

It is rare for letrozole to cause serious side effects but those that do occur are usually ulcers, blisters, and sore throat due to leucopenia; high fever with chills due to infection; jaundice due to hepatitis; throbbing, cramping pain with signs of inflammation due to thrombosis; and swellings of the face, lips and tongue causing dysphagia and dyspnea in case of an allergic reaction[19,25].

Regarding the efficacy of letrozole, studies have shown that this drug has maximum inhibitory effect on the estrogen levels[26]. Two comparative researches were conducted to study the effect of letrozole and clomiphene citrate in the induction of ovulation. One study revealed that 86.9% of the patients under letrozole ovulated during the observation period, whereas the other study showed it to be 62%[26,27]. Researchers that studied the successful pregnancies resulting from letrozole demonstrated that 43.8% to 58% of the patients reported pregnancies[28,29]. On the other hand, an independent study showed that only 14.7% of the cases had reported a pregnancy[26].

Letrozole is now the primary treatment for infertility, and when compared to the previous first-line treatment clomiphene citrate, Letrozole was noted to have a 13% increase in ovulation rate and an 8% increase in live-birth rate[20,23]. Although, other studies show that in terms of efficacy, letrozole and clomiphene citrate have no significant differences; yet letrozole has better pregnancy rates due to its advantage over improved endometrial thickness[27].

Gonadotropin

For a long time, we have had an understanding of how gonadal functions are controlled by the pituitary hormones known as gonadotropins[30]. These are peptide hormones that participate in regulating the ovarian and testicular functions. In women, these primarily coordinate the menstrual cycle[31].

Two pituitary-secreted hormones are FSH and LH. hCG is known to have a similar process comparable to LH surge[32]. These hormones create increased growth of primary follicles. The early phase of growth of the primary follicle till the antral stage is mainly accelerated by the FSH alone. Looking at LH, a surge of LH is necessary for ovulation. Despite having large quantities of FSH, follicles would not be able to advance to ovulation in the absence of LH[31].

Considering the physiology of gonadotropins, the clinical benefits are seen in ovaries, especially to induce ovulation in infertility treatments[32]. In 1927, Ascheim and Zondek discovered the presence of substances that stimulate the gonad in both the blood as well as urine of pregnant women which was the hCG[33]. Later Zondek hypothesized that two hormones secreted by the pituitary gland that both actively stimulate the gonads[34]. Based on the endocrine function they were named respectively as FSH and LH. The physiological function of these hormones suggested that they can be utilized for infertility treatment, eventually leading to the development of pure gonadotropin products[35].

Gonadotropin is well known as the secondary treatment for women with PCOS presenting with infertility. Both recombinant follicle-stimulating hormone (FSHr) and hMG are used as treatment options for time intercourse or intrauterine insemination[36]. The most commercially available preparation is human menopausal gonadotropin (hMG). This is also known as Menotropin or Pergonal. One ampule consists of LH activity of 75IU and FSH activity of 75IU[32].

Recombinant gonadotropins are also available. In addition, hCG is also used as it has a similar physiological action as LH. hCG is obtained from the urine of pregnant women and is available in ampoules with 1000-5000 IU[32]. The treatment protocol is heavily personalized to get the best results. The primary rule is a higher dosage given to women in cases of secondary amenorrhea due to pituitary failure and a lower dosage in cases of ovulatory failure and corpus luteal insufficiency[32].

In treatment with hMG, treatment is started following spontaneous menses or induced menses. For 5 days a daily dose of 1-2 ampoules is administered intramuscularly. This is either continued with the same dose or increased with a cervical mucus study, sonographic folliculometry at 2-3 days intervals, or till the preovulatory follicular diameters reach 18-20 mm.

hMg is then discontinued and hCG is administered intramuscularly for ovulation with a dose of 5000 IU[32].

The following are the conditions that contraindicate the use of gonadotropins treatment[32].

High levels of endogenous FSH, indicate ovarian failure; Ovaries cannot respond to the stimulation as they already have diminished function. Hence making the treatment useless and having potential risks. Overt thyroid or adrenal dysfunction; these conditions will alter with the hormonal balance necessary for ovarian stimulation. Pituitary tumors; can exacerbate the tumor's effects and cause more adverse reactions.

Indeterminate uterine bleeding; indicates further evaluation and management. Gonadotropins with timed intercourse produce an ovulation rate of about 70% and a clinical pregnancy rate of 20% with multiple births reaching up to 5.7%[36]. A study conducted comparing Letrozole and hMG for ovulation induction in clomiphene resistance PCOS patients, demonstrated a successful pregnancy rate of 27.1% in the hMG group[37].

DISCUSSION

The first-line management of infertility due to PCOS is non-pharmacological therapy such as increasing the physical activity and dietary habits in the patient[23]. Reducing weight through diet changes and regular physical exercise not only reduce hyperandrogenism, but even a 5-7% weight loss can reestablish consistent menstruation and improve ovulation and the response to ovulation-inducing agents[23]. The general recommendations on exercise for these patients include physical activity for a minimum of half-an-hour for at least, 5 days per week; with different durations and frequencies for vigorous exercises or when trying to achieve more modest weight loss[23]. Additionally, a cut of 500 to 750 kcal/day from their everyday diet should be implemented, although there are no specific dietary recommendations[23]. The second-line management includes induction of ovulation, as 70% of patients with PCOS have no ovulation (anovulation) or irregular ovulation (oligo-ovulation)[23]. Before proceeding with this line of treatment, other common causes of infertility should be evaluated by doing semen analysis and tubal patency testing. After careful evaluation, ovulation induction can be proceeded using the drugs; clomiphene citrate, letrozole, and gonadotropins[23].

Clomiphene citrate binds directly to the receptors of estrogen in the hypothalamus to promote the secretion of gonadotropin-releasing hormones and in turn increase the ovarian follicular activity[23,9]. Letrozole also has a similar end effect, however, it decreases estrogen levels by blocking the demethylation of androgens[22]. When comparing clomiphene citrate and letrozole, the ovulation rates between the two show no significant differences, albeit, the pregnancy outcome was notably higher in letrozole with 29% being pregnant while in clomiphene citrate 15.4% got pregnant. In the same study, similar differences were seen in live birth rates with letrozole having a rate of 25.4% and clomiphene citrate having a rate of 10.9%[38,39].

Regarding the side effects of using these medications, patients on clomiphene citrate report experiencing more side effects, while those taking letrozole complained little to none at all[40,41]. This could be due to letrozole's short half-life of approximately 45 hours[23]. Comparing the likelihood of multiple pregnancies between both the drugs, some studies found that the risk is lower in letrozole compared to clomiphene citrate while other studies show no significant difference[42]. Similarly, the abortion rates and congenital defects in children conceived via infertility treatment by using either letrozole or clomiphene citrate, showed no considerable differences between the two drugs[43]. Thus, letrozole is now being considered as the first-line treatment for ovulation induction in patients with infertility[20].

For the secondary treatment for induction of ovulation, the choice of drug is gonadotropins[23]. Administration of exogenous gonadotropins to promote follicular growth and different gonadotropin preparations can be used, as the efficacy; side effects and risk of multiple pregnancy rates between the options have no significant difference[23]. Although, the risk of ovarian hyperstimulation syndrome and multiple pregnancies are overall higher in patients taking gonadotropins, and thus gradual increase or gradual decrease protocols are used, along with careful ultrasound monitoring[23]. With timely intercourse, gonadotropins have an ovulation rate of 70%, with a 20% rate of pregnancy[36].

When administering gonadotropins, it can be given in combination with one of the first-line treatments as well. Studies have shown that gonadotropins given along with clomiphene citrate have a considerably higher pregnancy rate compared to administering letrozole alone[42]. Studies conducted with letrozole added to their gonadotropin treatments showed that the addition of letrozole results in fewer gonadotropin administrations, with no negative effect on pregnancy rates[44]. Letrozole combined with gonadotropins has also been proved to be effective in patients with clomiphene resistant infertility, and has also been proven to reduce the risk of hyperstimulation[45].

Metformin is another drug that could be used along with gonadotropins to improve ovulation, successful pregnancy rates and successful delivery of live fetes[23]. Metformin directly lowers androgen production in the ovaries, thus preventing ovarian hyperandrogenism that causes premature follicular atresia and anovulation[23]. However, metformin does cause some side effects in the alimentary tract such as abdominal discomfort, nausea, vomiting and diarrhea, and so should be administered initially at a lower dose of 500 mg and gradually increased up to a maximum dose of 1500 mg per week[23].

When pharmacological options fail, additional treatment options that could be considered includes Assisted Reproductive Technologies (ART) such as *in vitro* fertilizations, *in vitro* maturation and intracytoplasmic sperm injection; laparoscopic ovarian drilling; and bariatric surgery[23]. However, not much evidence is available regarding ARTs, and the evidence

on laparoscopic ovarian drilling and bariatric surgeries is of low quality[23].

CONCLUSIONS

PCOS remains as the most common hormonal disorders, due to its heterogeneous nature, many cases remain undiagnosed. This syndrome can affect different aspects of an individual, most importantly fertility. Letrozole is better than clomiphene citrate to induce ovulation and is the most promising drug for PCOS. Hence, letrozole is now the primary line treatment for PCOS for the patients that fail to achieve ovulation induction through selective estrogen receptor modulators and aromatase inhibitors, gonadotropin is recommended as a secondary treatment option for PCOS.

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AUTHOR'S CONTRIBUTION

Ibrahim AE: writing original draft, investigation. **Shareef FI:** formal analysis, data curation, conceptualization. **Yazdhan A:** writing, review and editing, methodology. **Shabin A:** formal analysis, data curation. **Ali PSS:** conceptualization. **Ahmad MP:** literature survey. Final manuscript was checked and approved by all authors.

DATA AVAILABILITY

The data will be available to anyone upon request from the corresponding author.

CONFLICT OF INTEREST

There is no conflict of interest.

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