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## Do Aromatase Inhibitors Offer Better Choice Than Selective Estrogen Receptor Modulators For Management Of Polycystic Ovarian Syndrome?.

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### Review Article

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#### ABSTRACT

Polycystic ovarian syndrome (PCOS) is responsible for 55% - 70% of infertility cases caused by chronic anovulation. Clomiphene Citrate (CC) is considered as first line drug for induction of ovulation in these patients. Aromatase inhibitor has been used as new drug for ovulation induction for last decade. There are many studies related to comparative use of CC and Letrozole but results are not consistent. To review the literature related to use of Letrozole and CC in infertile patient with PCOS to conclude, which is better ovulatory agent for the management of anovulation?. A search of English language literature was conducted using PubMed, Google Scholar, Cochrane database of systemic review and EMBASE databases. Old to most recent publications regarding Letrozole and Clomiphene for ovulation induction were reviewed. Evidences suggest that Letrozole (AI) may replace CC as a first line ovulation inducing agent in infertile patients with PCOS in the future. Many studies showed increased rates of ovulation and pregnancy with fewer side effects by Letrozole as compare to CC. But definitive studies in the form of randomized controlled trials comparing CC with AIs are needed.

#### INTRODUCTION

PCOS is a common endocrine disorder in reproductive age women (6.8%) [1,2] causing anovulation and infertility. It is responsible for 55-70% of infertility cases. This syndrome is characterized by irregular menstrual cycle, hirsutism, enlarged ovaries with multiple cysts and anovulation [3]. There are many drugs and treatment modalities available in the market for its treatment, but none of them give satisfactory results.

Clomiphene Citrate is a selective estrogen receptor modulator (SERM) used as first line drug for induction of ovulation in these patients for last many years. CC is very effective ovulation inducing agent with the advantages of being orally administered, relatively safe and inexpensive. In contrast, alternative treatments as gonadotropins are more complicated, given by parenteral route, expensive, and associated with serious complications. CC was also found to have adverse effects such as antiestrogenic endometrial and cervical mucus changes which could prevent pregnancy even in condition of successful ovulation [4].

It has been demonstrated by many studies that Letrozole, an aromatase inhibitor (AI) seems to be a promising alternative to CC for ovulation induction [5]. Purpose of this review is to outline the old and most recent data collected by author, regarding the use of Letrozole and CC for ovulation induction and help the clinicians for better management of infertility.

I will start the review with WHO classification of anovulation, the mechanism of action and problems with SERM as well as the mechanism of action and advantages of Als, with clinical studies regarding comparative use of CC and Letrozole for ovulation induction in infertility patients with PCOS and then discussion with conclusion and references.

### **WHO classification of Anovulation**

World Health Organization (WHO) divide the ovulation into three groups [6,7]. Group 1 disorders are due to hypothalamic-pituitary failure with deficient estrogen and normal or low FSH and prolactin levels. They typically have amenorrhea and require pulsatile GnRH infusions or injectable gonadotropins to ovulate. Group 2 disorders are due to hypothalamic-pituitary dysfunction. These patients are not estrogen deficient. Their FSH and prolactin levels are normal. They typically experience oligomenorrhea and anovulatory cycles. This is the most common type of ovulation disorder and includes polycystic ovary syndrome (PCOS). Group 3 disorders are due to ovarian failure. These patients have elevated gonadotropins secondary to primary ovarian failure mainly due to decreased inhibition of gonadotropins by follicular estrogen. They are resistant to various methods of ovarian stimulation and need oocyte donation. The present review will focus on the use of the CC and Letrozole, to induce ovulation in women with WHO group II anovulation.

### **Mechanism of action, dose and side effects of Clomiphene Citrate (SERM)**

Clomiphene citrate is still considered as first line therapy for induction of ovulation in infertile patients with PCOS [8,9]. It is a non-steroidal selective estrogen receptor modulator (SERM) *i.e.* exhibits both estrogen agonistic and antagonistic property. It acts mainly by binding on estrogen receptors at hypothalamus [10] which results in decreased follicular estrogenic negative feedback on hypothalamus. As a result, GnRH secretion increases which causes increase in FSH and LH secretion and subsequent induction of ovulation [11]. CC is administered orally, starts on 2<sup>nd</sup> to 5<sup>th</sup> day of menstrual cycle with starting dose 50 mg tab daily for 5 consecutive days [7]. The dose of CC can increase by 50 mg in subsequent cycle until ovulation is induced (max upto 6 cycles). Ovulation occurs successfully in 70-85% cases per cycle, while cumulative live birth rate 50-60% after CC treatment up to 6 cycles [12].

Although CC is a very good ovulation inducing agent, but it causes antiestrogenic effect on endometrium and cervical mucus that may prevent pregnancy even after successful ovulation. Because of its longer half life (5d to 3 wk [13], it accumulates in body for longer duration and causes many side effects. There are reported risk of ovarian hyper stimulation syndrome and multiple gestations due to augmentation of FSH by CC [14,15].

Exogenous gonadotropins can be given as second line drug for anovulation but there are highly increased chances of multiple pregnancy and ovarian hyper stimulation syndrome and require intense monitoring [4]. Because of these problems, the concept of aromatase inhibition was proposed as a new agent for ovulation induction to avoid many of the adverse effects of CC [16].

### **Mechanism of action, dose and advantages of Letrozole (Aromatase inhibitor)**

Aromatase is a microsomal cyochrome P450 hemoprotein containing enzyme. It is a product of CYP19 gene and catalyzes the synthesis of estrone and estradiol from androstenedione and testosterone respectively. Aromatase is found in many tissues, e.g. ovaries, breast, brain, liver, adipose tissues, liver and placenta etc. Estrogen is mainly formed in ovary in premenopausal women and adipose tissue in postmenopausal women [17]. This enzyme expressed in tissue specific manner. Letrozole is an aromatase inhibitor approved by FDA for breast cancer treatment. It is also being used successfully as an ovulatory agent in infertility patients due to PCOS since last decade [5,15]. Letrozole causes inhibition of aromatase and block the production of estrogen from all sources. This low estrogen causes decrease in feedback estrogenic inhibition on hypothalamus/pituitary axis resulting increase in gonadotropins which causes follicular growth and ovulation. The usual dose of Letrozole is 2.5mg to 7.5mg per day given from 3<sup>rd</sup> to 7<sup>th</sup> day of cycle [18].

As Als does not antagonize estrogen receptors in brain, normal central feedback mechanism remains intact, which limit the FSH response. Therefore less chances of multiple ovulation and hyper stimulation syndrome occurs by use of letrozole as compare to CC. Half life of letrozole is short (approx 45 hrs), so it is rapidly eliminated from the body [19] and causes less side effects. There is normal endometrial

development and thickness in Als treated women, so more chances of pregnancy in case of successful ovulation.

### Clinical studies of Clomiphene Citrate and Letrozole as ovulation inducing agents

Many relevant clinical studies are available comparing efficacy and side effects of Letrozole versus CC in PCOS patients. Mitwally and Casper conducted first clinical study of Als for ovulation induction in 2001 [20]. 22 infertile women who had failed to respond to CC were treated with 2.5 mg letrozole daily for 5 days. Ovulation observed in 75% patients and pregnancy was achieved in 25%. In another study of CC-resistant women with PCOS, letrozole induced ovulation in 54.6% and pregnancy in 25% patients [21]. Atay et al. (2006) conducted a clinical study on 106 women with oligomenorrhea and PCOS (55 received CC and 51 letrozole). Letrozole versus CC induced percentage of ovulatory cycles were 82.4% versus 63.6%, pregnancy rates 21.6% versus 9.1%, and endometrial thickness 8.4 mm versus 5.2 mm [22]. Usma and Ahmed (2011) conducted a randomised trial on 214 patients of unexplained infertility randomly divided the patients into two groups and treated with either letrozole for extended period (2.5mg/day from cycle day 1 to 9) or CC 100 mg/day from day 3 to 7. They observed higher pregnancy rates per cycle (18.96% Vs 11.43% ) and cumulative pregnancy rates (37.73% Vs 22.86%) in letrozole treated women as compared to CC. Endometrial thickness was also significantly higher in letrozole treated group<sup>5</sup>.

Kar S. conducted a comparative study of use of CC and letrozole on 103 infertile women with PCOS. Result demonstrated that letrozole use was associated with a similar ovulation rate (73.08% in the letrozole group versus 60.78% in the clomiphene group,  $P=0.39$ ) but significantly higher pregnancy rate (21.56% in the letrozole treated group versus 7.84% in the clomiphene treated group  $p=0.015$ ) [23].

Mohamad S. Abdellah demonstrated letrozole induced ovulation in 59% and pregnancy in 35.7% patients in clomiphene resistant PCOS women [24]. Another clinical trial demonstrated that upto 90% patients who failed to respond to CC were developed mature follicle and 25.94% patients became pregnant by letrozole. Majority of these ovulating women showed mono follicular ovulation [25]. The conclusion of review article written by Robert F Casper and Mohamed F.M. Mitwally (2006) was also in favour of Als as first line drug as compare to CC for Ovulation induction [7]. A randomized controlled trial on 217 women with unexplained infertility demonstrated significantly higher number of mature follicles in CC treated group as compare to Letrozole treated group ( $2\pm 0.9$  versus  $1\pm 0.0$ ,  $P=0.02$ ). The clinical pregnancy rate was significantly higher in letrozole group (23.07 vs 10.68%,  $P<0.001$ ). There was statistically significant increase in endometrial receptivity in letrozole treated group as assessed by endometrial thickness [26].

But few studies showed no significant differences in the efficacy of Als and CC. In the study of Bayar et al, differences between Letrozole and CC regarding ovulation rates (74.5% versus 65.7%) or pregnancy rates (7.4% versus 9.1%) were not found, although the percentage of monofollicular cycles was higher in letrozole treated women [27]. Badawy et al. studied 438 infertile women (1063 cycles) with PCOS. Patients were randomly received either 5 mg of letrozole daily (218 patients, 540 cycles) or 100 mg of CC daily (220 patients, 523 cycles). In this study there was no significant difference in ovulatory cycles, pregnancy rates or miscarriage rates between letrozole and CC treated group [28].

### DISCUSSION AND CONCLUSION

PCOS is a common endocrine disorder in childbearing age women. It is one of the most common causes of infertility due to ovulation defects. Ovulation induction is an essential therapy for these patients. There are many drugs and treatment procedures available for induction of ovulation in infertile women with PCOS examples: clomiphene, letrozole, metformin, gonadotropins, LOD (Laparoscopic ovarian drilling), FSH, GnRH agonist, cauterization and wedge resection of the ovaries, and assisted reproductive technology [29].

Among oral agents, Clomiphene Citrate is still considered to be a first-line treatment for induction of ovulation in PCOS. But there are many side effects of CC like antiestrogenic effect on endometrium and cervical mucus that may be a cause of low rates of pregnancy even after successful ovulation. There are reported cases of ovarian hyper stimulation syndrome and multiple gestations with the use of CC. Many women showed Clomiphene resistance during infertility treatment. Clomiphene resistance is defined as three cycles of failure to ovulate or six cycles of ovulation without pregnancy [30].

Recently, letrozole has been proposed as effective medication and is being used for induction of ovulation in PCOS patients. It has less adverse effects and more pregnancy rates as compare to CC.

Letrozole can also induce ovulation and pregnancy in clomiphene-resistant patients as in above mentioned studies. It can be because of its beneficial effect on uterine endometrium which helps in improvement of rate of implantation and pregnancy in case of CC resistance. So Letrozole can be recommended for patients who ovulate with clomiphene but have a thin endometrium. Several studies also found that the effectiveness of letrozole was comparable to that of combined CC and gonadotropin for the induction of ovulation in PCOS infertile patients [31]. The Combination of letrozole and clomiphene can be used in both drug resistant cases as formation of dominant follicles in 82.9% and pregnancy in 42% of resistance cases was observed in one study [32].

In conclusion, Letrozole can be considered an alternative to clomiphene for inducing ovulation in PCOS patients and assisted reproductive field because of more pregnancy rates and low chances of multiple ovulation, hyperstimulation syndrome, endometrial and other side effects. But because the result of few studies are not consistent, properly designed randomized clinical trials are required to confirm whether letrozole can be introduced as a first line treatment (superior to CC) in infertility patients with PCOS.

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