

## **Comparison of letrozole with gonadotropins and letrozole\_gonadotropin combination for ovulation induction in PCOS women after clomiphene citrate failure**

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### **Abstract**

The aim of this study is to compare the efficacy of letrozole with gonadotropin and letrozole plus gonadotropin for ovulation induction in PCOS women after clomiphene citrate failure, Seventy eight women with PCO failed to conceive with clomiphene citrate divided in to three groups A,B,C treated with letrozole tablet, , letrozole plus follicular stimulating hormone and follicular stimulating hormone injection alone respectively for ovulation induction..Results: ovulation rate was (65.4%),(76.9%) and(76.9%) in group A,B &C respectively, pregnancy rate in study groups were (50%),(69.2%)and(65.4%) in A,B,&C respectivelyConclusion: Letrozole appears to be a suitable ovulation inducing agent in PCOS women with CC failure and significant higher pregnancy rate was observed in letrozole co treatment with gonadotropins as compared to other two protocols

***Key ward:Letrozole , follicular stimulating hormone,infertile women, PCOS***

## **Introduction**

Polycystic ovary syndrome is a silent epidemic; leading cause of infertility in women due to anovulation Syndrome<sup>1</sup>. 20-25% of Polycystic ovary syndrome women are resistant to clomiphene citrate and fail to ovulate, in such cases the traditional option is to administer gonadotropins.<sup>2</sup> The concept of using aromatase inhibitors(AIs) as a new method of ovulation induction has been extensively investigated by several research groups in the past few years<sup>(3,4,5,6)</sup>. During the past decade, Letrozole has been successfully used for induction of ovulation in an ovulatory patient with Polycystic ovary syndrome(PCOS) and for augmentation of ovulation in ovulatory women<sup>(7,8)</sup>. Letrozole a highly selective AIs has been found to be effective in inducing ovulation in anovulatory and ovulatory infertile women with inadequate response to clomiphene citrate.<sup>(9,10)</sup> Several studies revealed that Letrozole can be used as an alternative to clomiphene citrate for superovulation in patient with unexplained infertility.<sup>(11,12)</sup>

Letrozole is as effective as clomiphene citrate in inducing ovulation, but is devoid of antiestrogenic side effects, result in lower serum estrogen concentrations and is associated with good pregnancy rate and potentially a lower incidence multiple pregnancy than clomiphene citrate. When combined with gonadotropins for assisted reproductive technologies(ART), Letrozole reduced the dose of FSH required for optimal follicle recruitment and improve the response to FSH in poor responders.<sup>4</sup> Because of relatively long half-life of clomiphene citrate isomers, clomiphene citrate may exert an avoidable antiestrogenic effects on peripheral estrogen targets (endocervix and endometrium) that likely explain the absence of pregnancy despite ovulation observed in some CC treated patients.<sup>(4)</sup> However, clomiphene citrate

induces prolonged estrogen receptors depletion and therefore exerts antiestrogenic effect on estrogen target tissues as endocervix and endometrium.<sup>(13,14)</sup> Letrozole is rapidly eliminated from the body and does not deplete estrogen receptors and therefore has no adverse effect on endometrium or endocervix.<sup>(15,16)</sup> We postulated that it would be possible to block estrogen negative feed back without depletion of estrogen receptors as occur with clomiphene citrate by administration of aromatase inhibitors in the early part of menstrual cycle, both circulating estrogen (produced by ovarian follicles and peripheral conversion of androgens in fat and other tissues) and locally produced estrogen in brain exert negative feedback on gonadotropin release.<sup>(17)</sup> A second hypothesis that may add to mechanism of action of AIs in ovarian stimulation involves an increase follicular sensitivity to FSH, this could be result from temporary accumulation of intraovarian androgens because conversion of androgen substrate to estrogen is blocked by aromatase inhibition.<sup>(4)</sup> Several research groups have observed a higher pregnancy rate with gonadotropin therapy as compared to oral ovulation inducing agents in women failing to conceive with CC.<sup>(7,18)</sup> Letrozole treatment was shown to be more cost-effective than FSH alone in patients undergoing controlled ovarian stimulation and intrauterine insemination.<sup>(19)</sup> As a result of the mechanism of action of AIs, the present study proposed that AIs could be used alone for induction of ovulation or as adjuvant in conjunction with exogenous FSH or other medications to improve the outcome of ovarian induction.

## **Patients and Method**

A prospective study, including 78 infertile women with PCOS diagnosed by the

Rotterdam criteria.<sup>(20)</sup> who failed to conceive or ovulate despite 3cycles of clomiphene citrate using 100mg/ day and showed poor endometrial development (endometrial thickness ` 0.7cm )were seen in Tikrit teaching hospital between July 2010 to March 2012. In this study the treatment protocol was planned in to three groups : **Group A:** 26 women received letrozole 2.5mg twice daily starting from day 3 of menstrual cycle for 5 days. **Group B:** 26 women received letrozole 2.5mg twice daily and two ampoules of 75IU of follicle-stimulating hormones on day 3 and other on day 8 of cycle. **Group C:** 26 women were continuously received one ampule of 75IU follicular stimulating hormones, daily from day 2 of cycle onwards until the day of HCG administration

All patient were monitored by ovarian follicular development and endometrial thickness by transvaginal ultrasound from day 8 on ward ,10,000IU HCG administered as a single dose when average diameter of follicles reach `18mm. Tubal patency and male partner semen were evaluated, the patients were counseled about the benefit and the risks of Letrozole and gonadotropins treatment. Ovulation rate and pregnancy rate were compared amongst the three groups.

**Results**

The age of patients ranged from 21 to 38 years with a mean 26.8 years. (28.2%) with primary infertility & (71.8%) with secondary infertility, the duration of infertility was ranged from 3-9 years. Ovulation rate and pregnancy rate were lower in primary infertility than in secondary infertility as shown in tables (2),(3)

**Table (1):- Method of work**

<i>Study groups</i>	<i>No.</i>	<i>Type of drug</i>	<i>Dose</i>
<b>Group A</b>	26	Letrozole tablet	2.5mg twice
<b>Group B</b>	26	Letrozole tab+Gonadotropin (FSH)	2.5mg twice & tow Gonadotropin ampules 75IU *
<b>Group C</b>	26	Gonadotropin ampoules (FSH)	Gonadotropin ampoules 75IU
<b>Total</b>	78		

The ovulation rate was 65.4%,76.9% and76.9% in group A,B &C respectively, Ovulation rate was similar in Letrozole plus FSH and FSH only cycle, while pregnancy

rate was more in Letrozole plus FSH group. We found that pregnancy rate in study groups were (50%),(69.2%)and(65.4%) in A,B,&C respectively

**Table (2):- Ovulation rate in study groups**

Type of infertility	Ovulation	Group A	Group B	GroupC	Total
Primary	Yes	5(71.4%)	5(71.4%)	6(75%)	16(72.7%)
	No	2(28.6%)	*2(28.6%)	2(75%)	6(27.3%)
<b>Total</b>		7(100%)	7(100%)	8(100%)	22(100%)
Secondary	YES	12(63.2%)	15(78.9%)	14(77.7%)	41(73.2%)
	No	7(36.8%)	4(21.1%)	4(22.3%)	15(26.8%)
<b>Total</b>		19(100%)	19(100%)	18(100%)	56(100%)

**Table (3):- Pregnancy rate in study groups**

Type of infertility	Pregnancy	Group A	Group B	GroupC	Total
Primary	Yes	3(42.8%)	4(57.2%)	6(75%)	13(59%)
	No	4(57.2%)	3(42.8%)	2(75%)	9(41%)
<b>Total</b>		7(100%)	7(100%)	8(100%)	22(100%)
Secondary	YES	10(52.6%)	14(73.6%)	10(55.5%)	35(62.5%)
	No	9(47.4%)	5(26.4%)	8(44.5%)	21(37.5%)
<b>Total</b>		19(100%)	19(100%)	18(100%)	56(100%)

We have three cases of multiple pregnancy one case triplet and two cases of twin pregnancy. All of third group C (continues FSH)

## **Discussion**

Several investigators have documented the feasibility, safety and effectiveness of aromatase inhibition for ovulation induction.<sup>(21)</sup> Casper has stated that Letrozole has a potential role as a first line oral therapy for ovulation inductions in women with PCOS.<sup>(22)</sup> The pregnancy rate in present study was 50%,69.2%&65.4% and ovulation rate was 65.4%,76.9%&76.9% In group A,B,andC respectively ,this is good agreement with recent reports which conclude that letrozole has a better ovulation and pregnancy rate in patients with PCOS.<sup>(23,24)</sup> There are , significantly higher pregnancy rates reported with gonadotrp in than with letrozole alone<sup>(25,26)</sup>. Several studies revealed that the combination of exogenous gonadotropins with Letrozole increase the number of mature oocytes and therefore improve the outcome of IUI cycle<sup>(7,11)</sup>. The addition of gonadotropins to Letrozole is accompanied by a more ovarian response than the use of Letrozole alone, this may be attributed to the fact that Letrozole temporarily inhibit the production of estrogen which activates gonadotropin and in turn stimulates follicular growth.<sup>(27)</sup> Letrozole administration in early follicular phase blocks estrogen syntheses, and causes temporary accumulation of androgens in ovarian follicles , the accumulation of androgens may increase the sensitivity of the growing follicles to FSH by increasing the expression of FSH receptors.<sup>(28)</sup> In the present study gonadotropin alone or in combination with letrozole appears to be the most effective protocol, and pregnancy rate in group B (Letrozole &FSH) was observed to be slightly higher as compared to group

C(FSH) ,this consist with Goswami etal.<sup>(3)</sup>. There were no multiple gestation case s among pregnancies that occurred with letrozole and letrozole FSH co treatment, this consist with Mitwally etal .<sup>(9)</sup>.

## **Conclusion**

Letrozole appears to be a suitable ovulation inducing agent in PCOS women with CC failure and significant higher pregnancy rate was observed in letrozole co treatment with gonadotropins as compared to other two protocols

## **Recommendation**

Letrozole co treatment with gonadotropins best ovulation protocol for infertile PCOS woman after clomiphene citrate protocol failure

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