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Comparison of Clomiphene Citrate and Letrozole for Ovulation Induction and Resultant Pregnancy Outcome

Selvaraj *Kamala*, Selvaraj *Priya*
Fertility Research Centre, GG Hospital, 6E, Nungambakkam High Road, Chennai 600 034.

OBJECTIVE – To determine the pregnancy outcome with letrozole as an ovulation inducing agent in infertile patients. **METHOD** – A Randomized clinical trial was conducted on 250 infertile patients attending the outpatient department. Letrozole was administered as 5 mg tablets from day 3 to 7 of menstruation after a preliminary day 2 LH level and baseline ultrasound. **RESULTS** – Letrozole given alone had a poor outcome of eight pregnancies with two miscarriages. Letrozole with clomiphene citrate (CC) yielded the best results with no pregnancy wastage. There was a marginal improvement in the endometrial response. Polycystic ovarian disease (PCOD) cases resistant to CC responded better. **CONCLUSIONS** – Letrozole did not prove better than CC or gonadotropins except in few cases of PCOD. It can be tried prior to usage of CC in PCOD and for those with a poor implantation site. The best method of usage of letrozole as a first line therapy in anovulatory and ovulatory infertility is to be determined by future research.

Key words : letrozole, follicular growth, endometrial response, pregnancy outcome

Introduction

The most popular drug used in ovulation induction is clomiphene citrate (CC) followed by gonadotropins or a combination of both. Though CC gives good ovulation, the pregnancies achieved are much lower than expected[1], probably due to the adverse effect it has on the implantation site.

Gonadotropins are associated with multiple follicular development, sometimes ending in conversion of an IUI cycle to one of IVF-ET. It also has a higher risk of ovarian hyperstimulation[2].

Clomiphene Citrate

CC has been the most commonly used drug for ovulation induction in the past decades[3]. Several hypotheses explain the mode of action of CC, but its mechanism and site of action still remain to be clarified. The overall mechanism seems to be the sum of its effects on the hypothalamus, pituitary and ovary[4].

Though good ovulation rates can be achieved by CC, pregnancy rates are much lower, only about 20 – 40% [5]. There is also a higher incidence of miscarriage[6].

This contradiction in the ovulation and pregnancy rates can be attributed to the antiestrogenic effect of CC. Due to its long half-life and slow clearance, it persists in the body for a long time and adds to the accumulation of the antiestrogenic effects[7,8].

The antiestrogenic effect of CC can be overcome either by administering estrogen concomitantly or by administering CC earlier than on day 5, so that the antiestrogenic effect is allowed to subside. CC can also be combined with an estrogen receptor modulator – this has more estrogen agonistic effect. However, none of the above methods completely avoid the antiestrogenic effect of CC[9]. Moreover, resistant cases need a higher dosage.

An alternative to CC had been gonadotropins. But they are associated with multiple pregnancy and ovarian hyperstimulation syndrome (OHSS)[10].

Aromatase contains enzyme complex that catalyzes the rate-limiting step in production of estrogens. It is a good target for selective inhibition because estrogen production is the terminal step in the biosynthetic sequence. Letrozole (Femara, Novartis) is a selective aromatase inhibitor. Aromatase activity is present in many tissues, such as the ovaries, adipose tissue, muscle, liver, breast tissue and malignant breast tumors. Aromatase inhibitors, in the ovary, increase follicular sensitivity to FSH. The conversion of androgen substrate to estrogen is blocked, resulting in accumulation of intra-ovarian androgens. This stimulates insulin like growth factor – I (IGF-I), which along with other endocrine and paracrine factors, synergizes with FSH to promote folliculogenesis.

By a short-term administration of aromatase inhibitors in the early follicular phase, the negative feedback of estrogen is removed and gonadotropins secretion is indirectly increased from the pituitary, thus

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Correspondence :
Drl Selvaraj Kamala
Fertility Research Centre, GG Hospital. 6E, Nungambakkam High Road. Chennai 600 034, Tamil Nadu, India.
Tel. 2827 7563, 2822 2460

successfully stimulating follicular growth. Letrozole is a highly specific and potent non-steroidal aromatase inhibitor. It is hypothesized that letrozole administration in the early part of the menstrual cycle would release the pituitary / hypothalamic axis from estrogenic feedback. This is similar to the effect of CC but the depletion of endometrial response and the adverse endometrial and cervical mucus effects that are usually associated with CC are not seen here.

The estradiol level during ovarian induction with letrozole is significantly lower when compared with the other stimulation protocols. Such a reduction may be contributory, in part, to pregnancy rates.

However, till now there are no studies, which have reported the effects of long-term use of aromatase inbibitors on human follicular growth[11].

This study tries to compare letrozole, an aromatase inhibitor, and CC for ovulation induction and campares outcomes of resultant pregnancies.

Material and methods

The study was conducted over a period of one year from 1stAugust 2002 to 31 July 2003. A total of 250 patients were included in the study. They comprised of idiopathic infertility (41), male infertility (45), PCOD (69), endometriosis (24), PID (33), PID with endometriosis (26) and fibroid (12) cases. Apart from the need for ovulation inducation there were no other selection criteria. The patients had a preliminary work up consisting of semen analysis for the male and day 2 LH and prolactin, baseline sonogrpahy and diagnostic laparoscopy for the female.

A day 2 LH level was determined and if below 6 IU, patients were given letrozole (5 mg) from day 3 to day 7. Follicular study was conducted from day 9 onwards. If there were no dominant follicles the patients were now given CC in doses of 200 mg for 5 days or hMG150 IU on alternate days till the follicles started to develop. When the dominant follicle reached 20 x 20 mm the patients were given hCG 10,000 IU for further maturation and rupture. The patients, then, underwent intrauterine insemination (IUI), one day before and one day after the rupture.

Results

Out of the 250 patients enrolled in the study, 31 became pregnant of which five carried their pregnancy to term, another five had miscarriages and the remaining 21 have ongoing pregnancy.

Use of clomiphene citrate alone

We administered CC in the form of Triple Regime, which consists of CC (starting from 50 mg), dexamethasone (0.5 mg) and conjugated estrogen (0.625 mg). A random analysis of ovulation induction with CC in 48 women showed a mean number of mature follicles of 6, the range varying from 3 to 13. The mean level of estradiol on the day of hCG administration was 1002.3 pg/ml, the lowest being 565.07 and the highest 2952.35. The mean endometrial response (ER) was 9 mm. There was little or no improvement in the ER after hCG administration. Only 13% of patients showed 70 to 80% increased ER while most of them exhibited the same value even after hCG administration. Occurrence of OHSS was 6%. Pregnancy percentage was 37.5% and the miscarriage rate was 25%.

Use of letrozole alone

Out of 250 patients, 118 were given only letrozole 5mg per day from day 3 to 7 of the cycle. Analysis of ovulation induction with letrozole showed a mean number of mature follicles of 4, the range varying from 0 to 7. Twenty of the cases had no follicles. The mean level of estradiol on the day of hCG administration was 692.66 pg/ml, the lowest being 122.3 and the highest 1165.63. The mean ER was 9 mm. There was no improvement in the ER after hCG administration. There were no cases of OHSS. Follicular studies between days 9 and 14 showed either no dominant follicles or one or two measuring 19 x 19 mm. Not much difference was seen in the effect of CC and of letrozole on endometrial growth. Out of the 118 patients, only 8 pregnancies were achieved, of which, two had missed abortion and six are ongoing.

Use of letrozole with clomiphene citrate

The combination of letrozole and CC was given as an initial dose of letrozole from days 3 to 7 and a step up with CC (200 mg/day) from day 9 or 10 for 5 days. There were a total of 16 patients in this series, and nine achieved pregnancies. All the nine pregnancies are ongoing.

The rest of the patients were on different regimes – like combination of letrozole with other stimulation drugs, FSH and gonadotropins.

The effect of letrozole on patients with and without PCOD was compared. There were 69 patients who had PCOD. Ovulation induction with letrozole showed an average of 3 follicles, (range 1 to 5). The mean level of estradiol on the day of hCG administration was 775.72 pg/ml (range 511.06 to 1020.89). The mean endometrial response was 7 mm, which rose to 10 mm after hCG administration. Out of the 69 patients, 15 (21.73%) got pregnant, of whom 5 (33.3%) have delivered, 2 have (13.3%) ongoing

Table I. Performance of letrozole alone and with other drugs for ovulation induction

Drug	No. of Patients	No. of Pregnancies	Ongoing	Pregnancies Wastage	Delivered
Letrozole	118	8 (6.7%)	6	2	-
Letrozol + gonadotropins	60	8 (13.3%)	4	3	1
Letrozol + FSH + CC	56	6 (10.7%)	2	-	4
Letrozol + CC	16	9 (56.2%)	9	-	-
Total	250	31	21	5	5

Table II. Camparison between letrozole alone and clomiphene citrate alone

	Letrozole	Clomiphene citrate
No. of patients	118	48
Number of follicler - range (mean)	0 – 7 (4)	3 – 13 (6)
Estradiol level (pg / ml) - range (mean)	122.3 – 1165.63 (692.66)	565.07 – 2952-35 (1002.3)
Endometrial response (mean)	9 mm	9 mm
ER after hCG admin.	**No improvement**	**Little /no improvement**
OHSS	Nil	3 (6%)
Total no. of pregnancies	8 (6.7%)	18 (37.5%)
Wastages	2 (1.6%)	12 (25%)

pregnancy and 8 (53.3%) have miscarred.

Discussion

Aromatase inhibitors were first described for the management of symptomatic leiomyoma[11]. Mitwally and Casper[12] used them for ovulation induction and reported 75% success when letrozole was used.

In our center, we found that letrozole worked better than CC in many of the PCOD cases. Patients with PCOD, who failed to ovulate or whose endometrial response was inadequate when put on CC, responded well to letrozole.

Patients who had poor implantation sites (i.e ≤ 7 mm endometrial thickness) when treated with CC had a two months break for its effects to subside and then were given letrozole. There was an improvement in the implantation site from 7 to 9 mm and even 10 mm in few cases. When letrozole was administered, there were only two or three dominant follicles thereby minimizing risk of OHSS.

However, when success rate of letrozole was compared with that of CC, its performance was not satisfactory. Letrozole when given alone had a poor outcome – out of the 118 patients, only eight showed positive results. Letrozole with FSH and CC was effective in that there was no pregnancy wastage. Comparatively, a combination of letrozole with CC yielded better results.

The other advantage of the drug was that there was no fetal malformations. However, an overall fetal wastage of 16.1% is reported in our center, which is undeniably high when compared to the lower wastage with letrozol.

Performance of letrozole as an invididual stimulant for ovulation is yet to be proved. Sufficient affirmative data are not available to assert the positive effects of the drug on associated factors like the implanation site or the ER as is being suggested by some researchers. Longer accumulation of CC in the body due to its long half-life[8] causes deleterious effects. But letrozole is hypothetically not supposed to result in any such side effects due to its shorter half-life[13].

Aromatase inhibitor has a terminal half-life of 45-50 hours. Administering the aromatase inhibitor, letrozole, as a single dose on day 3 of the menstrual cycle would have the advantage of allowing its rapid clearance from the body due to its shorter half-life. It is cleared from the circulation by the liver long before the critical period of embryogenesis.

Recent opinions suggest that the drug when used for purposes other than treatment of breast cancer can cause serious side effects like ovarian tumors, liver cancer and sexual inactivity. However, no such effect was seen in any of our patients, nor in their fetuses, during our short study. A few adverse effects, gastrointestinal disturbances being the most prevalent (24/250;9.6%) asthema (9/250;3.6%), hot flushes (2/250;0.8%), headache (15/250; 6%), backache (19/250;7.6%) and thinning of hair (15/250;5.2%) were observed.

We have found through our experience that when day 2 LH is more than 6, the quality of the oocyte is poor. Pregnancy does not occur and even if it does, it ends in missed abortion. So, we generally prefer to check day 2 LH.

Aromatase inhibitor, letrozole, when put into clinical trial for induction of ovulation and pregnancy outcome, did not prove better than CC in most of the cases, except for a few selected cases of PCOD.

Letrozole can be tried initially for two to four cycles before switching over to CC especially for those patients with poor implantation site.

With our experience, we opine that there is no special advantages of this drug over CC and the superiority of the drug is yet to be established.

References

1. Mitwally MF, Casper RF Aromatse inhibition for ovarian stimulation, future avenues for infertility management. *Curr Opin Obstet Gynecol, 2002; 14: 255-63.*
2. Shrivatsav P. Aromatase inhibitors – their role in the treatment of infertility. *The art and science of ART. 2003; 7: 47-9.*
3. Franks S, Adams J, Mason H et al. Ovulatory disorders in women with polycystic ovary sydrome. *Clin Obstet Gynecol 1985; 12: 605-32.*
4. Adashi EY. Clompihene citrate:mechanisms and sites of action: a hypothesis revisited. *Fertil Steril 1984; 42: 331-44.*
5. Garcia J, Jones GS, Wentz AC. The use of Clomiphene Citrate. *Fertil Steril 1977; 28: 707-17.*
6. Goldfarb AF, Morales A, Rakoff AE et al. Critical review of 160 Clomiphene – related pregnancies. *Obstet Gynecol 1968; 31: 342-45.*
7. Young SL, Opsahi MS, Fritz MA. Serum concentrations of enClomiphene and zuClomiphene across consecutive cycles of Clomiphene Citrate therapy in anovulatory infertile women. *Fertil Steril 1999; 71: 639-44.*
8. Mikkelson TJ, Kroboth PD, Cameron WJ et al. Single dose pharmacokinetics of clomiphene citrate in normal volunteers. *Fertil Steril 1986; 46: 392-44.*
9. Wu CH, Winkel CA. The effect of therapy initiation day on Clomiphene Citrate therapy. *Fertil Steril 1989; 52: 564-68.*
10. Hurst BS, Tjaden BL, Kimbali A et al. Superovulation with or without intrauterine insemination for the treatment of infertility. *J Reprod Med 1992; 37: 237-9.*
11. Shozu M, Murakami K, Segawa T et al. Successful treatment of a symptomatic uterine leiomyoma in a perimenopausal woman with a nonsteroidal aromatase inhibitor. *Fertil Steril. 2003; 79: 628 31.*
12. Mitwally MF, Casper RF. Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to Clomiphene Citrate. *Fertil Steril, 2001; 75: 305-9.*
13. Mirwally MF, Casper RF. Aromatase inhibition reduces gonadotrophin dose required for controlled ovarian stimulatioin in women with unexplained infertility. *Hum Reprod. 2003; 18: 1588-97.*