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A PROSPECTIVE STUDY TO COMPARE THE EFFICACY OF LETROZOLE AND CLOMIPHENE CITRATE IN OVULATION INDUCTION IN POLYCYCTIC OVARIAN SYNDROME WITH CLOMIPHENE RESISTANCE

Obstetrics & Gynaecology

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ABSTRACT

Objective: To compare the effectiveness of letrozole and clomiphene citrate in induction of ovulation in infertile patients with PCOS with clomiphene resistance.

Design : A prospective randomized control study

Study population : Sixty : Four anovulatory patients with PCOS, who fail to ovulate on taking 50 mg/day of CC for two cycles.

Intervention : Patients were randomly divided into two groups, one group received 2.5 mg/day of Letrozol another group received 100 mg of CC, starting from day third of menstrual cycle for five days for three to six months depending upon the response . Results analysed in terms of occurrence of ovulation , endometrial thickness and achievement of pregnancy

Result : Twenty (62.5%) patients from letrozole group and 12 patients (37.5%) from the CC group ovulated during the ovulation period. Mean serum E2level was 817.75 pg/ml and 444.03 pg/ml in CC and letrozol group respectively. Thirteen patients from letrozol group (40.63%) and six patients (18.75%) from CC group attained conception

Conclusion : Aromatase inhibitors like letrozole, are safe and superior to CC in terms of ovulation induction and achieving successful pregnancy in patients with poor response on low doses of clomiphene with PCOS

KEYWORDS

INTRODUCTION

Polycystic ovarian syndrome, affecting 5- 10% of women represents one of the most common endocrinological disorder in women of reproductive age. 70% of anovulatory infertility has been found to be associated with PCOS. Fertility treatment option for women with PCOS centers around treating anovulation using various drugs. Clomiphene citrate is considered the first line ovulation induction drug for anovulatory infertility. Clomiphene citrate is a selective estrogen receptor modulator acting on hypothalamic pituitary axis, hence the negative feedback for gonadotropin is blocked due to inhibition of estrogen receptors at hypothalamus level. Gonadotropin release is enhanced, thereby accelerating follicular development. Usual starting dose of clomiphene is 50mg per day for 5 days starting from second or third day of menstrual cycle. Depending upon the response dose may be increased in 50 mg increments each cycle for a maximum of 150 mg. About 75 to 80 % of women achieve ovulation with Clomiphene citrate but successful pregnancy rate is only 22% per cycle. This discrepancy between ovulation and pregnancy has been attributed to the antiestrogenic effect of CC on endometrial receptivity.

Letrozol is an aromatase inhibitor which blocks the conversion of androgen to estrogen in the ovarian follicles, peripheral tissue, and brain. The resultant decrease in estrogen level releases hypothalamic pituitary ovarian axis from negative feedback of estrogen. Increased FSH results in normal follicular growth, selection of dominant follicles and atresia of smaller growing follicles, hence facilitating a monofollicular growth and ovulation. Letrozole use has been associated with reduced chances of ovarian hyperstimulation syndrome and multiple gestation.

Chances of clinical pregnancy and live birth has also been found to be higher with letrozole then CC. The aim of our present study is to find if letrozole is a better alternative for ovulation induction in PCOS patients who are poor responders.

MATERIALAND METHOD

The study was conducted in Department of Obstetrics and Gynaecology, Patna medical college & hospital, PMCH, Patna, Bihar, as a prospective randomized controlled trial between May 2018 to February 2019.

Sixty four anovulatory patients with PCOS who fail to ovulate on taking 50 mg of clomiphene citrate for 5 days in two consecutive cycles were the target population for the study. Polycystic ovarian syndrome was diagnosed by Rotterdam criteria. Patients who have hyperprolactinemia, thyroid disorder, male factor infertility, known or suspected tubal factor infertility (endometriosis and pelvic inflammatory disease) and unexplained infertility were excluded from the study. Patients not developing follicles of optimum size (17mm) by day 16 of the CC cycle were recruited for the study. Patients were divided by lottery to receive either 100 mg of CC daily or 2.5 mg of letrozole daily for five days starting from day three of the cycle. Follicular monitoring was done by transvaginal ultrasonography on day 10, 12, 14 and 16 of cycle untill a mature follicle was detected. Follicle was considered mature when it attained a diameter of 18 mm or more by averaging inner two diameter of the follicle. To evaluate physiological maturity, serum E2 was measured when the follicle was assumed to be anatomically mature. A level of 100 pg/ ml of E2 was considered satisfactory. A single injection of 10,000 hCG was given if at least one follicle attained 18 mm diameter. Transvaginal sonography was done after 48 hrs of hCG injection to observe ovulation. If the follicle was found unruptured, a third TVS was done after 72 hrs of hCG injection to observe a luteinized unruptured follicle (LUF). Ovulation was ascertained by observing rupture of the dominant follicle on ultrasound and day 21 progesterone level. A progesterone level of 10 ng/ml suggested ovulation. Endometrial thickness was measured in the plane of central longitudinal axis of the uterus, at a point of maximum distance between the echogenic interface of the diameter. A trilaminar daimeter of 8 mm or more was considered a satisfactory responses. The main outcome was rate of ovulation and pregnancy. Two consecutive cycle were observed to declare ovulation failure. Six ovulatory cycle were observed for pregnancy.

RESULTS

Characteristic of age, duration of infertility and basal hormone levels(Table 1) were similar in both grops of patients. Mean age was 25.47± 3.98 years and 26.09± 3.62 years, duration of infertility was 2.66± 1.11 years and 2.58±1.10 years in the letrozole and CC groups respectively. Average follicular diameter on day 16 of the cycle was 18.84 ± 3.17 mm(range 14- 23 mm) in letrozole group and 16.19± 3.47 mm (range 12- 22 mm) in CC group which shows significant difference in rate of follicular size on day 16 of the cycle (P value < 0.05). On the day of Hcg injection the mean E2 level was significantly higher in CC group (817.75±286.70pg/ml) than in letrozole group (444.03±85.42pg/ml). (p value <0.05). Mean endometrial thickness was higher in letrozole group (10.37±1.2mm) then in CC group(9.03±0.89 mm; p value < 0.05). Mean day 21 serum progesterone level was higher in letrozol group(19.09± 10.47 ng/ml)

then in CC group (13.90± 12 ng/ml). In this study ovulation was significantly more frequent in the letrozole group (62.5 %; 20 patients) then in CC groups (37.50 % ; 12 patients)($p < 0.05$). pregnancy rate was although higher in letrozole group (40.62%) then in clomephene group (18.75%) the difference was not significant.in both the groups there is a significant positive correlation between endometrial thickness and pregnancy rate(r= 0,64, p= 0.00 in letrozole group, r= 0.73, p=0.00 in CC group) and between progesterone level and pregnancy rate(r= 0.43, p= 0.013 in letrozole group, r= 0.50, p=0.004 in CC group. Two patients had blighted ovum in letrozole group but none occurred in CC group

Table -1 : patients characteristics

characteristics	Letrozole (mean ± SD) N= 32	CC (mean ± SD) N= 32	P value
Age in years	25.47± 3.98	26.09± 3.62	0.38
BMI (kg/m2)	22.72±2.77	23.63±3.23	0.12
Duration of infertility (years)	2.66± 1.11	2.58±1.10	0.69
Basal hormone on day 3			
FSH	6.09± 1.37	5.79±1.60	0.43
LH	8.54±2.58	8.73±2.15	0.74
E2	58.94±16.79	57.59±17.07	0.71
TSH	4.63±0.32	4.53±0.46	0.42
Prolactin	23.40±4.9	22.91±5.06	0.74

Table 2-Response to treatment

Parameters	Letrozole (n=32)		CC(n=32)		
	Mean ± SD	Range	Mean ± SD	Range	
DOMINANT FOLLICULAR DIAMETER ON DAY 16 (mm)	18.84±3.17	14-23	16.19±3.47	12-22	<.001
Serum E2 on day of Hcg administration Pg/ml	444.03±85.42	310-650	817.75±286.70	55-1,232	<.001
Endometrial thickness on day 16 (mm)	10.37±1.2	8-12	9.03±0,89	7-14	<.001
Serum progesterone level on day 21 (ng/ml)	19.09±10.47	3-37	13.90±12	2-35	<.05

Table 3; development of follicles by day 16 in both groups

Follicular size	Letrozole		CC	
	n	%	N	%
10- 13 mm	0	0	7	21.88
14 -17 mm	12	37.50	13	49.63
18- 19 mm	5	15.62	7	21.88
20– 22 mm	12	37.50	5	15.63
• 22 mm	3	9.38	0	0

Table 4 : Outcome of ovulation induction

parameters	Letrozole		CC		P value
	n	%	N	%	
Ovulation	20/32	62.50	12/32	21.88	<0.05
Pregnancy	13/32	40.62	6/32	49.63	> 0.05
Pregnancy among ovulatory patients	13/20	65	6/12	21.88	> 0.05

DISCUSSION

Clomephene citrate is the most commonly prescribed medication for ovulation induction when women are anovulatory. The antiestrogenic effect of CC produces cervical mucus thickening and thinning of the endometrium. Inappropriate development of endometrium is associated with low implantation rate and early pregnancy loss due to leutal phase defect. Approximatly 20- 25% of patients do not respond to CC and doses higher than 150 mg is not recommended. In CC unresponsive cases the next step for induction of ovulation is the use of gonadotropins which increases both the cost and risks associated with treatment. Letrozole, which is an aromatase inhibitor, has the same role as 'CC in initiating gonadotropins release through the withdrawal of its negative feedback on the pituitary by reducing blood E levels.

Clomephene citrate blocks the ERS, creating a false impression of a deficient E environmen the pituitary. On the other hand letrozole makes an E deficient environment by blocking the conversion of androgen to estrogen. Hence the initial release of FSH may be more than in case of CC. Letrozole has however has an added positive effect, because peripherally it may increase follicular sensivit to FSH through amplification of FSH receptor gene expression. Although creates an estrogen deficient environment, it has no negative effect on the endometrium and cervix due to its short half life. In present study 62.50 % of patients achieved ovulation with letrozole as compared to only 21.88 % with 100 mg CC in poor responder patients with PCOS. The difference being significant. Another significant advantage noted with the use of letrozole was pronouncd monofollicular development, thereby reducing the chances of multiple pregnancy. Only five patients (25%) developed more than one follicle in letrozole cycle, where as nine patients (75%) patients had more than one follicle development in CC cycle. More number of patients developed follicles of 20 -22mm diameter with letrozole than in CC group. In CC treated cycles the mean E2 level was significantly higher than letrozole cycle. But, when calculating only mature follicle, per follicle E2 level were 410 pg/ml in CC group and 325 pg/ml letrozole group, which does not show a significant difference. Endrometrial thickness and serum Progesteron level were higher in lerozole group . Although the E2 level was higher in the CC group the mean endometrial thickness and progesterone level was lower, probably due to fewer ovulatory patients. Use of letrozole was associated with minimal side effect like transient headache and occasional feeling of lack of energy which is minimal as compared to other ovulation inducing drugs.

CONCLUSION

The result of this small prospective study suggested that aromatase inhibitors like letrozole, are safe and superior to CC in terms of ovulation induction and achieving successful pregnancy in patients with poor response on low doses of clomiphene with PCOS. Letrozole should be considered safe and better alternative for ovulation induction in such patients before embarking on expensive and risky gonadotropins.

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