ORIGINAL ARTICLE

Efficacy of Letrozole as First Line Ovulation Induction Agent in Subfertile Women

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ABSTRACT

Aim: To determine the efficacy of letrozole, an aromatase inhibitor as a first line ovulation induction agent in subfertile women

Patients and Methods: This prospective study was conducted among 120 subfertile women. Letrozole was given as 2.5 mg twice daily dose from day 3 to day 7 of menstrual cycle. Follicular growth was monitored on ultrasound. Fertile period explained to couple. hcG given on follicular growth of 19-22mm. Pregnancy was confirmed by urine test when cycle became overdue and later confirmed by ultrasound.

Results: Out of 120 patients follicular growth occurred in 108 patients (90%), pregnancy occurred in 48 patients (40%). Three patients had miscarriage (2.5%) per cycle pregnancy rate. None had hyperstimulation syndrome or multiple gestation.

Conclusion: Letrozole may be considered as safe and effective first line drug for ovulation induction with minimal side effects.

Keywords: Letrozole, ovulation induction, infertility.

INTRODUCTION

Anovulatory dysfunction is a common problem and is responsible for about 50% of female infertility. Ovulation induction is the method for treating anovulatory subfertility, once ovulation is achieved pregnancy can be achieved.[1] In subfertile women undergoing ovulation induction clomiphene citrate has long been used as drug of choice for first line treatment. The drug works primarily by competitively inhibiting the binding of Estradiol to its receptor in the hypothalamus. Thereby releasing the hypothalamus from negative inhibition and allowing increased release of follicular stimulating hormone from pituitary gland. This increased FSH release enhances follicular growth, increasing the chance of ovulation.

Letrozole, a third generation selective Aromatase inhibitor has been found an effective treatment for fertile women with anovulation. It prevents the conversion of androgen to estrogen thus releasing the hypothalamo-pituitary axis from negative feedback of estrogen resulting in increased FSH secretion from anterior pituitary leading to ovulation. The accumulated androgen in ovary further increases follicular sensitivity to FSH.[2] Letrozole appears to have less adverse effects on endometrium which are frequently associated with clomiphene citrate during ovulation induction.[3] Letrozole does not antagonize estrogen receptors in brain, the initiating of follicular growth producing increase concentration of both estradiol and inhibin results in normal secondary feedback loop that limits FSH response thus avoiding the risk of ovarian hyperstimulation syndrome and multiple pregnancy.[4] Importantly unlike clomiphene citrate, letrozole is devoid of any antiestrogenic peripheral action. Letrozole is also cleared from circulation more rapidly due to shorter half-life (48 hours) as compared to clomiphene citrate which may take up to 2 months due to its prolonged half-life (2 weeks).[5] The main interest of study to assess the efficacy of letrozole as first line drug in terms of follicular growth, number of follicles, pregnancy rate and miscarriage in infertile patients with anovulation.

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PATIENTS AND METHODS

The study was conducted at Seyal Medical Centre Multan from June 2012 to May 2013. One hundred and twenty women with primary subfertility were enrolled in study. Primary subfertility was confirmed by taking history. Detailed history about menstrual cycle was taken. After explaining and taking consent, clinical examination including general appearance, height, weight, BMI, blood pressure, hirsutism, thyroid gland, breast and pelvic examination was done.

RESULTS

Regarding age-wise distribution, 48 (40%) patients were of 18-25 years of age, 60 (50%) patients belonged to 26-30 years of age and 12 (10%) patients were 31-35 years of age. Most frequent age group was 26-30 years of age. The mean age of patients was 25.92±3.92 years. Age of patients ranged 18-35 years (Table 1). Table 2 showed the body mass index (BMI), 65 (54%) had 20-25 k/m^2, 49 (41%) had 26-30 kg/m^2 and 6 (5%) had >30 kg/m^2. The normal BMI was 54, with increased BMI was 41% and 5% patients were obese. Ninety (75%) patients had duration of infertility 1-4 years and 30 (25%) patients had duration of infertility of 5 years or more than 5 years (Table 3). Follicular growth was seen in 108 (90%) patients. There was no mature follicular growth in 12 (10%) patients. Pregnancy occurred in 48 (40%) patients out of 120 (Table 4). About 20 (41%) of patients became pregnant in age group of 18-25 years, 18 (37%) patients in age group of 26-30 years and 10 (21%) patients became pregnant in age of 31-35 years (Table 5). In relation to duration of subfertility, 38 (42%) patients became pregnant in whom duration of subfertility was 1-4 years and 10 (33%) patients were those whom duration of infertility was 5 years or more than 5 years (Table 6). In relation to BMI, 30 (47%) patients became pregnant with BMI 20-25 kg/m^2, 17 (35%) patients became pregnant with BMI 26-30kg/m^2 and 1(17%) patient became pregnant with BMI 30-35 kg/m^2 (Table 7).

Table 1: Age-wise (n=120)

Age (years)	=n.	%
18 – 25	48	40.0
26 – 30	60	50.0
31- 35	12	10.0

Table 2: Frequency of body mass index (n=120)

Body mass index	=n.	%
Normal (20-25 kg/m^2)	65	54.0
Increase (26-30 kg/m^2)	49	41.0
Obese (>30 kg/m^2)	6	5.0

Table 3: Distribution of cases according to duration of subfertility (n=120)

Duration of subfertility	=n.	%
1- 4 years	90	75.0
≥5 years	30	25.0

Table 4: Efficacy of letrozole (n=120)

Outcome	=n.	%
Follicular growth	108	90.0
Pregnancy	12	10.0

Table 5: Pregnancy in relation to age-distribution

Age (years)	Total patients (n=120)		Pregnancy (n = 48)	
	No.	%	No.	%
18 -25	48	40.0	20	41.0
26 - 30	60	50.0	18	37.0
31- 35	12	10.0	10	21.0

Table 6: Outcome in relation to duration of subfertility

Duration of subfertility	Total patients (n=120)		Pregnancy (n = 48)	
	=n.	%	=n.	%
1- 4 years	90	75.0	38	42.0
≥5 years	30	25.0	10	33.0

Table 7: Outcome in relation to body mass index

Body mass index	Total patients (n=120)		Pregnancy (n = 48)	
	=n.	%	=n.	%
20-25 kg/m^2	65	54.0	30	47.0
26-30 kg/m^2	49	41.0	17	35.0
>30 kg/m^2	6	5.0	1	17.0

DISCUSSION

Infertility is a common clinical problem all over the world including our country. It contributes a considerable work load on gynecologists. Two thousand gynaecological patients visited of which 260 were infertility. One hundred and twenty patients were with primary subfertility. So frequency of infertility in our area is 13% similar to results as described by Padubidri and Daftary Shirish[6].

In this study we used letrozole as first line ovulation induction agent because of several advantages[7] high pregnancy rate, monofollicular ovulation, lesser chances of multiple gestation and ovarian hyperstiumulation syndrome, 100% bioavailability after oral administration and rapid clearance from body so less likely to have antiestrogenic effects on endometrium and cervical mucus.

Aromatase inhibitors are non-steroidal compounds that suppress estrogen biosynthesis by blocking the action of enzyme, aromatase, which converts androstenedione and testosterone to estrogen. It is given in a dose of 2.5-5 mg/day and has been shown to achieve optimal suppression of serum estrogen level and is almost free of side effects[8,9].

In our study we gave, letrozole in dose of 5mg/day, same dose was given in study conducted at Department of Obstetrcis & Gynecology, All India Institute of Medical Sciences (AIIMS), New Delhi, India[10] and another study conducted at KPC Medical College India[1]. Pregnancy rate after taking 5mg of letrozole is 40% out of 129 patients. Results in our study were

better than results observed at KPC Medical College Kolkata India in 2011 with conception rates of 27.3% after taking 5 mg of letrozole.[1] The results of our study were almost same as results of international study conducted at New Dehli India on July 2012 in which pregnancy rate was 43.8% after taking 2.5-5 mg of letrozole.[10] Results were 26.3% in one study conducted at Department of Obstetrics and Gynaecology, McGill University, Montreal, Quebec, Canada in which two doses of letrozole were compared and pregnancy rates were higher in dose group of 5 mg as compared to 2.5 mg.[11] Casper[12] has stated that letrozole has potential role as first line agent in patients with PCOS. In our study most frequent age group was 26-30 years of age with 60 patients (50%) and 18-25 years of age with 48 patients (40%). In the present study, most of populations were younger. Similar observation was made in an international study in Kolkata, India.[1]

In the present study, 54% patients had normal BMI, 41% patients had increased BMI, 5% patients were obese. Anovulation is the most common cause of infertility. In our study letrozole was given in obese patients and patients with normal BMI. Pregnancy rate were more in normal BMI patients as shown by results in study of New Dehli India.[10] Duration of subfertility was mostly 1-4 years in 75% patients and more than 5 years in 25% patients. We observed monofollicular growth in our patients, similar observation was made by Bayar et al[13] and Atay et al[14].

CONCLUSION

It is free of side effects on endometrium and cervical mucus, it has shorter half-life. Letrozole is increasingly becoming a drug of choice as first line ovulation induction agent.

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