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Original Research Article

# Evaluation of Letrozole as Suitable Ovulating Induction Agent in Patients with PCOS Induced Infertility

**Pratima Kumari[1], Sangita Kumari[2]**

**[1]Assistant Professor, Department of Obstetrics & Gynecology, Nalanda Medical College and Hospital, Patna, Bihar, India.**

**[2]Assistant Professor, Department of obstetrics & Gynecology, Nalanda Medical College and Hospital, Patna, Bihar, India.**

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**Corresponding author: Dr. Sangita Kumari**
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**Abstract**

**Aim:** To compare the pathological nature of infertility amongst the female population in the Indian subcontinent.

**Material & Method:** The main source of data for this study are the women with primary and secondary infertility with anovulation attending the Department of Obstetrics & Gynecology, Nalanda Medical College and Hospital, Patna, Bihar, India. This is a prospective study with a total of 200 women satisfied the inclusion and exclusion criteria of the study. The present study consists of cases of infertility due to anovulation which were thoroughly evaluated before the diagnosis of anovulation was confirmed.

**Results:** In this study mean age of the patients were 28.0 years and mean age of husbands were 32.4 year. 105 patients underwent diagnostic hysterolaparoscopy with chromopertubation + ovarian drilling.

**Conclusion:** Letrozole can be considered as suitable ovulating induction agent in patients with PCOS induced infertility. It is a better drug in terms of mono follicular ovulation and better endometrial thickness than other ovulation induction agents. It has high ovulation rate with significant conception rate, with only drawbacks being miscarriages.

**Keywords:** Infertility, PCOS, Letrozole



## Introduction

In 1986, a new compound was tested by Ciba-Geigy (later Novartis) in an in vivo assay (1). This compound, CGS 20267, now known as letrozole, was a third-generation, nonsteroidal aromatase inhibitor [1]. Letyrozole was approved to be effective for a wide range of breast cancer settings, which at present it's only registered indication [2]. In 1993, letrozole was initially used in animal ovulation induction (OI) [3]. In 2000, the first pilot study for the clinical use of letrozole for OI indicated a high rate of ovulation in polycystic ovary syndrome (PCOS) patients [4].

Polycystic ovary syndrome (PCOS) is undisputedly the most common gynecological endocrinopathy [5]. Although PCOS is underdiagnosed [6], its prevalence ranges between 2.2% and 26%

in different countries [7], and 6.8–18% in women of reproductive age, using different diagnostic criteria and recruitment method of the study population. The primary clinical indicator of PCOS is irregular or lack of menstrual cycles and infertility. There is a clear link between PCOS and infertility, as PCOS is responsible for 55% to 70% of infertility cases resulting from chronic anovulation, thus, it is among the most common causes of infertility due to ovulation dysfunction [8]. Although, around 60% of those with PCOS are considered fertile [9].

A variety of factors may affect normal fertility including patient's age, anatomy, ovulatory status and sperm quality. The potential causes of infertility can be divided into male factor and female factors [10]. Female factor infertility can be due to multiple causes like ovulatory factor, tubal factor, uterine factor, pelvic factor, decreased ovarian reserve and others. The gynecologist's initial encounter with the infertile couple is extremely important because it determines subsequent evaluation and treatment. Factors from either or both partners may contribute to difficulties in conception therefore it is important to consider all possible diagnosis before pursuing further management [11].

Additionally, hysteroscopic guided biopsy and therapeutic procedures like polypectomy, myomectomy, septal resection and adhesiolysis can be done in the same sitting. The main advantages of diagnostic laparoscopy over traditional open laparotomy are reduced mortality, decreased postoperative pain and shorter hospital stay. Studies have shown that diagnostic laparoscopy is effective as it reveals abnormal findings in 21.68% of cases after normal hysterosalphingography. Also, diagnostic hysteroscopy is a very important method for evaluation of causes of female infertility which is accurate, expeditious, cost-effective, dependable and minimally invasive [12].

Patients living in low resource rural areas find it difficult to seek healthcare related to infertility because of treatment costs, long duration of therapy, frequent visits to hospitals and need to travel long distances for expensive interventions. Thus, we aim to compare the pathological nature of infertility amongst the female population in the Indian subcontinent.

**Material & Method:**

The main source of data for this study are the women with primary and secondary infertility with anovulation attending the Department of Obstetrics & Gynecology, Nalanda Medical College and Hospital, Patna, Bihar, India for one year. This is a prospective study with a total of 200 women satisfied the inclusion and exclusion criteria of the study. The present study consists of cases of infertility due to anovulation which were thoroughly evaluated before the diagnosis of anovulation was confirmed.

**Inclusion Criteria:**

1. Patients with infertility due to PCOS.
2. Patients of age group 20-35 years will be included in the study.

**Exclusion Criteria:**

1. Patients with liver diseases.
2. Patients with kidney diseases.
3. Patients with hypothyroidism/hyperthyroidism/any other thyroid disorders.

**Methodology**

In each patient a detailed history was taken and the proforma of the same is attached. A detailed general examination was done. Examination of the breasts to rule out galactorrhoea, hair distribution and examination of thyroid gland was done. Cardiovascular and respiratory system were examined in detail. Abdominal examination was done for any evidence of tenderness or mass in the iliac fossa and

suprapubic regions. Pelvic examination consisted of speculum examination and bimanual examination to note the position of the uterus and for any adnexal enlargement and tenderness. Routine investigations such as CBC, VDRL, HIV, HBsAg, blood grouping and Rh typing, urine analysis, thyroid function test and semen analysis of husband were done in all cases. Special investigations like prolactin & FSH levels were done in few cases and were within normal limits.

**Laparoscopic chromopertubation:**

A semen analysis was done as a routine in all cases to rule out a male factor contributing to infertility. Hormonal estimations i.e. FSH, LH, prolactin were not done on routine basis. Secondary outcome measures are- pregnancy rate, miscarriage rate & failure rate.

Follicular study will be done by TVS from day 9 onwards by the same observer on alternate days. Recruitment of couple will be done following inclusion criteria after informed consent. Previously treated cases with failed clomiphene citrate induction will also be taken. Couple counselling will be done for timed intercourse/ IUI with evidence of rupture. Dominant follicle of 1.8-2.2 cm will be taken as standard & inj hCG 5000 IU will be given followed by timed intercourse 24-36 hours after documenting rupture.

Patient will be asked to follow up if she misses her period or evidence of menstruation. The primary outcome measures are- Dominant follicle, ovulation rate, endometrial thickness & development of adverse effects. We have routinely monitored the patients of either group by USG for a period of 3 to 6 cycles. In the absence of menstruation, diagnosis of pregnancy was detected by urine pregnancy test & confirmed by TVS and if pregnancy found negative, patient was given progesterone induced withdrawal bleeding and was asked to continue the same treatment from day 3 of the cycle and if menstruation occurs, one more course of the same was given and the treatment was given for a maximum of 3 to 5 consecutive cycles. Patients who did not respond to Letrozole alone, for them letrozole 2.5 mg was given from D2-D6 & injection human menopausal gonadotrophin (hMG) 75/150 IU on D3.

**Statistical Analysis:**

Categorical variables were represented in the form of frequency and percentage. Association between variables was assessed with Chi Square test. Continuous variables were represented using mean & Sd. Unpaired t test was used to compare the mean difference between groups. P value of <0.05 was considered statistically significant. Statistical analysis was done with IBM SPSS Version 22 for windows.

**Results:**

In the present study majority of the patients were between 25-29 years old, the minimum age was 18 years & maximum age was found to be 48 years. The anovulation was more common in age group of 25-29 years, which is the commonest period of maximum fecundity. In this study mean age of the patients were 28.0 years and mean age of husbands were 32.4 year. Hence this study shows maximum ovulatory cycles were common in age group 25.8 + 5.0.

In the present study, out of 200 cases; 165 cases were of primary infertility & 35 patients were of secondary infertility.

In our study, out of 200 subjects; 105 patients underwent diagnostic hysterolaparoscopy with chromopertubation + ovarian drilling. Out of 105 patients; 30 patients had bulky ovary and all the patients had features of PCOS and 3 patients had right fallopian tube block (Table 1).

The study shows that out of 200 patients 16 patients developed an average of less than 1 dominant follicle i.e. occasional an ovulatory cycle, 156 patients developed an

average of 1 dominant follicle i.e. 1 dominant follicle per cycle, & 28 patients developed an average of more than 1 follicles i.e. more than 1 dominant follicle in occasional cycle (Table 2).

In our study out of 200 patients who were induced with letrozole 188 patients achieved ovulation in 1st cycle of treatment. While 12 patients didn't achieve ovulation in 1st cycle of treatment. So, Ovulation during 1st cycle of treatment was 95.24%. In our study, out of 200 patients 48 patients conceived after induction with letrozole. Hence in our study the conception rate was 18.0%. (Table- 3).

**Table 1: laparoscopic findings**

| Laproscopic findings | | Frequency |
|---|---|---|
| Uterus | Normal | 131 |
| | Arcuate | 3 |
| | Bicomuate | 1 |
| | Not done | 65 |
| Ovary | B/L PCOS | 105 |
| | Bulky | 30 |
| | Not done | 65 |
| Tubes | Rt. Tube block | 3 |
| | Normal | 132 |
| | Not done | 65 |

**Table 2: average no. of dominant follicles per cycle**

| Avg. No of dominant follicle | Frequency |
|---|---|
| 0 | 16 |
| 1 | 156 |
| 1.1 – 2 | 28 |
| Total | 200 |

**Table 3: ovulation in 1st cycle of treatment**

| Ovulation in 1st cycle of treatment | Frequency |
|---|---|
| Yes | 188 |
| No | 12 |

**Discussion:**

Franik et al. [13] reported in The Cochrane Library. The analysis revealed the number of mature follicles to be similar in both treatment groups. This peculiar result may be explained by the fact that it was not the total number of follicles that was accounted for rather, it was the number of mature follicles sought. Meaning, although CC might have led to a higher number of follicles, it is conceivable that not all of them exceeded 18 mm in diameter.

Adverse events were hardly discovered and cited by most of the included studies. Though, Begum et al. [14] reported that two patients had 'blighted ovum' in the letrozole group, while Davar et al. [15] merely stated that there were two adverse events in the letrozole group without really specifying what they were exactly. Legro et al. [16] reported three serious adverse events linked to ovarian-cyst formation; two with letrozole and one with CC. Finally, most of the included studies made no mention of any major congenital

anomaly or harmful effects of the therapies to the newborns. Dehbashi et al.[17]detected one major congenital anomaly, meningomyelocele, in the CC group, while Legro et al. [16] identified five major congenital anomalies (4 with letrozoleand 1 with CC) but found no significant difference (P = 0.65) between the groups.[16]

Maruf Siddiqui et al. Conducted a study at the centre for assisted reproduction (CARE), BIRDEM in between August 2007 to December 2008. Polycystic ovarian syndrome patients were diagnosed using Rotterdam ESHRE/ASRM-consensus workshop group, 2004 criteria. 60anovulatory PCOS patient were then selected all of whom were previously treated with 150 mg of clomiphene citrate (CC) for at least 4 cycles with an inadequate outcome (no mature follicles/endometrial thickness of <= 0.7 cm). Patients with abnormal serum testosterone level/abnormal prolactin level/abnormal thyroid function tests. Study showed that Letrozole can be used as a relative inexpensive oral agent with reasonable success rate. It would be an excellent alternative for patients in developing countries.[18]

The non-oestrogenic effect of letrozole could have caused the lower multiple pregnancy rates observed in the letrozole group, even though statistically, no difference was found between the two treatment groups which might be related to the small number of events in both groups. However, it also confirms that monofollicullar ovulation was established in the majority of the induced cycles in either group. The analysis also suggested no statistically significant difference in miscarriage rate between the two treatment groups although there was slightly higher number of miscarriages in the group treated with letrozole. Interestingly, sensitivity analysis revealed that higher quality studies show superior effects of the intervention. However, more studies are needed because no clear inferences can be drawn by pooling the effects of only two studies.

ATAY et al., [19] 2006 assessed the efficacy of Als for 01 compared with CC. 106 women with oligomenorrhoea and PCOS were enrolled. Results were more favourable in the Letrozole group than in CC group regarding the percentage of ovulatory cycles (82.4% Vs. 63.6%), pregnancy (21.6% Vs9.1%), mono follicular cycles (1.2 Vs. 2.4 follicles > 18 mm on the day of HCG administration) and endometrial thickness (8.4 mm Vs. 5.2 mm). In our study though we have achieved 95.45% (105 patients) ovulation only 19% (21 patients) cases conceived. [20]

## Conclusion:

Letrozole can be considered as suitable ovulating induction agent in patients with PCOS induced infertility. It is a better drug in terms of mono follicular ovulation and better endometrial thickness than other ovulation induction agents. It has high ovulation rate with significant conception rate, with only drawbacks being miscarriages.

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