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# AN OBSERVATIONAL ANALYSIS OF CLINICAL PROFILE ASSOCIATED WITH OVULATION INDUCTION USING LETROZOLE AMONG INFERTILE WOMEN WITH POLYCYSTIC OVARIAN SYNDROME

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**ABSTRACT** **Background-** Polycystic ovary syndrome (PCOS) is major endocrine and metabolic disease in reproductive women. As per latest procedures, letrozole should be taken as the first-line pharmacological treatment for infertile women with PCOS. This study was planned to study the role of clinical profile in ovulation induction after letrozole therapy among infertile women with polycystic ovarian syndrome. **Methods-** This was a prospective analytical observational study carried out at the IVF centre, SMS Medical College, Jaipur. The present study enrolled 100 patients attending the IVF centre for fertility treatment who were diagnosed with PCOS as per Rotterdam criteria. Anthropometric measurements like Body mass index (BMI calculated as weight in kilograms divided by square of height in meters) and waist circumference (the smallest circumference at the level of umbilicus) was taken. A comprehensive physical examination of all patients was done to note signs of clinical hyperandrogenism like acne, alopecia, and hirsutism. Treatment response was defined as ovulation in response to letrozole in doses from 2.5 mg to 7.5 mg. **Results-**In this study, women from 20 to 25 years of age with shorter duration of infertility, lower BMI, lower waist circumference, absence of hirsutism, or mild hirsutism on clinical examination showed better response to Letrozole. **Conclusion-** Letrozole can be considered a suitable ovulation induction agent in infertile PCOS patients with lower BMI, lower waist circumference, and absence of hirsutism. A predictive ovulation score can be developed from basic clinical parameters. Identification of various factors affecting response to letrozole may help the clinician to individualize ovulation induction protocols in PCOS women.

**KEYWORDS :** BMI, Infertility, PCOS, Ovulation Induction, Letrozole

## INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a common endocrinopathy of reproductive age women characterized by oligo-ovulation or anovulation, signs of androgen excess, and multiple small ovarian cysts. PCOS affects approximately 4-12% of reproductive-age women.[1] Although symptoms of androgen excess may vary among ethnicities, PCOS appears to equally affect all races and nationalities. According to Rotterdam criteria, [2] women must have two of three criteria, after exclusion of other androgen excess related disorders among affected individuals:

1. Oligo and/ or anovulation,
2. Hyperandrogenism (clinical and/or biochemical)
3. Polycystic ovaries identified sonographically.

This triad of symptoms commonly accompanied in PCOS is obesity, insulin resistance, and infertility. Women with PCOS are also at increased risk of diabetes mellitus, endometrial carcinoma, and cardiovascular disease.[3] PCOS is a common cause of anovulatory infertility and requires treatment for anovulation. Many treatment options are available including weight reduction, ovulation induction, laparoscopic ovarian drilling, and assisted reproductive techniques. Induction of ovulation can be done by letrozole, clomiphene citrate, and gonadotropins[4]. Recently letrozole has emerged as a good option, with its oral route of administration, cost-effectiveness, shorter half-life, and negligible side effects[5].

To date, very few studies have been done in the state of Rajasthan to identify factors associated with response to ovulation induction using letrozole among infertile women with PCOS. This study was done to predict ovulation with the presence or absence of certain clinical profile of infertile women with PCOS. Establishing such an association will help the clinician in individualizing the best treatment for the patient thereby benefiting the patient in terms of both time and money.

## MATERIAL AND METHODS

This was a prospective analytical type of observational study, carried out at the IVF center of SMS Medical College, Jaipur. This study was conducted for a period of one year from May 2020 to April 2021. We enrolled 100 women with WHO-Group-II PCOS. The methodology was approved by the Doctoral Research Committee. Before the initiation of this study, approval was obtained from the institutional Ethical Committee (369/MC/EC/2021) dated 25/03/2021.

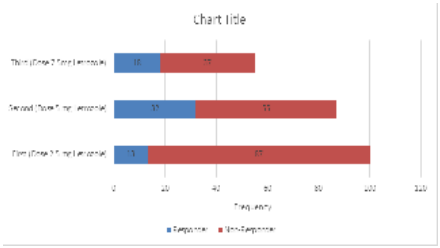
***Study Population***- Women attending the IVF OPD for treatment of infertility, diagnosed with PCOS as per Rotterdam criteria. Women in the age group of 18-35 years, having at least one patent tube and normal semen analysis of husbands who gave informed consent were included in the present study. Women with a history of ovarian surgery, chemotherapy or radiotherapy /or having any endocrine or systemic diseases /or using currently or have used in the last 3 months oral contraceptive/ glucocorticoids/ antiandrogens/ any ovulation-inducing agents, were excluded from the study. A detailed history was taken followed by a clinical examination of all study participants. All patients were examined on day 2 or 3 of spontaneous or induced menstrual bleeding. Anthropometric measurements like Body Mass Index (BMI calculated as weight in kilograms divided by square of height in meters) and waist circumference (the smallest circumference at the level of umbilicus) was taken. A comprehensive physical examination of all patients was done to note signs of clinical hyperandrogenism like acne, alopecia, and hirsutism. Grading of the scale of hirsutism was done as per the standard Ferriman Gallway score. After recording the patient's characteristics, letrozole was started at an initial dose of 2.5 mg on day 2 or 3 of the menstrual cycle. Follicles were monitored with serial USG till 1or 2 follicles reached ≥18 mm in size and endometrial thickness ≥8mm. Once this was achieved, the HCG trigger was given in the dose of 5000 IU by intramuscular route. After 35 to 36 hours, ovulation was confirmed with rupture of preovulatory follicles. If ovulation did not occur, the dose was increased from 2.5 mg to 7.5 mg during the subsequent cycles. Treatment response was defined as ovulations in response to letrozole in doses from 2.5 mg to 7.5 mg. Patients were followed up for three cycles and if there was no ovulation, they were defined as letrozole resistant.

***Statistical Analysis*:** The data was entered in a predesigned proforma in an excel spreadsheet (version Microsoft office 19). Nominal/ categorical variables were summarized as proportions and were analysed by using Chi-square/Fischer exact test. Continuous variables were summarized as Mean and Standard Deviation. Unpaired tests and parametric tests were used for the analysis of continuous variables. p-

value<0.05 was taken as significant. Medical 16.4 version software was used for all statical calculations.

## RESULTS

**Figure 1-** Participants' Response To Ovulation With Different Doses Of Letrozole




(Figure 1) depicts response in the study participants with increment in a dose of Letrozole according to cycle which was 2.5mg for the first cycle, 5mg for the second cycle, and 7.5mg for the third cycle. Out of 100 women, around two-thirds 63% (63/100) showed successful ovulation and 37% (37/100) failed to ovulate after the third cycle.

**Table 1- General Characteristics Of Study Participants**

| Variables | Responder (n=63) | Non-Responder (n=37) | P-value |
|---|---|---|---|
| Age (Years) | 26.04 ± 4.4 | 27.15 ± 3.60 | 0.197 |
| BMI (kg/m2 ) | 26.2 ± 2.3 | 31.5 ± 3.3 | <0.001(S) |
| Waist circumference (Cm) | 79.4 ± 4.2 | 92.2 ± 7.6 | <0.001(S) |
| Duration of Infertility (Months) | 21.3 ± 3.91 | 22.7 ± 4.56 | 0.107 |

(Table 1) In the present study, the BMI and waist circumferences of responders were significantly lower than the non-responders (p value<0.05). While the mean age and duration of infertility of responders were also lower than non-responders but the difference was statistically insignificant (p>0.05).

**Table 2- Difference In Clinical Hyperandrogenism In Responders And Non-Responders To Ovulation**

| Variables | Responder (n=63) | Non-Responder (n=37) | P value |
|---|---|---|---|
| Type of infertility (Primary) | 47(74.6) | 21(56.8) | 0.104 |
| Irregular menstrual characteristics | 52(82.5) | 31(83.8) | 0.908 |
| Acne | 9(14.3) | 4(10.8) | 0.849 |
| Alopecia | 4(6.3) | 3(8.1) | 0.942 |
| Acanthosis Nigricans | 3(4.8) | 2(5.4) | 0.739 |
| Hirsutism | 27(42.9) | 28(75.7) | 0.003 |

(Table-2) In the responder group, around three fourth 74.6% (47/63) of women had primary infertility, and the rest of 25.4% (16/63) had the secondary type of infertility whereas, among non-responders, 56.8% (21/37) had primary infertility and rest 43.2% (16/37) had secondary infertility. There was no significant difference in the type of infertility between responders and non-responders (p-value > 0.05). The proportioning of women who had acne among responders was higher than non-responders, although this difference was statistically insignificant (p-value > 0.05). The proportion of women who had hirsutism among responders was lesser than non-responders and this difference was statistically significant (p-value < 0.05). While Alopecia and Acanthosis Nigricans were higher among non-responders and this difference was statistically insignificant (p-value > 0.05).

**Table 3- Difference In Endometrial Thickness With Increasing Dose Of Letrozole**

| Cycle | Responder (n=63) | Non-Responder (n=37) | p-value |
|---|---|---|---|
| First (Dose 2.5 mg Letrozole) | 6.3 ± 0.8 | 6.09 ± 0.6 | 0.170 |
| Second (Dose 5 mg Letrozole) | 6.6 ± 0.7 | 6.2 ± 0.7 | 0.007(S) |
| Third (Dose 7.5 mg Letrozole) | 6.8 ± 0.8 | 6.5 ± 0.8 | 0.063 |

(Table-3) shows the response to letrozole on mean endothelial thickness (mm) in the study participants. With the increase in the dose of letrozole, mean endometrial thickness increased in both responders and non-responders. Mean endothelial thickness was significantly more in responders than non-responders at 5 mg dose of Letrozole (p-value < 0.05) The difference in endometrial thickness in both the groups at 2.5 mg & 7.5mg dose of Letrozole was found to be statistically insignificant (p-value > 0.05).

## DISCUSSION-

Infertility is seldom if ever a physically debilitating disease. In the past, clomiphene citrate was considered the drug of choice for ovulation induction, but now letrozole has taken its place. Clomiphene citrate (CC) has a better ovulation rate but, is not equally successful in all situations. It has many anti-estrogenic effects which ultimately cause poor endometrial response and other effects like Ovarian hyperstimulation syndrome, multiple pregnancies, etc. Alternative treatments to Clomiphene Citrate with drugs such as letrozole have attracted attention. Recently, Letrozole has been increasingly used for ovulation induction because of its less anti-estrogenic & systemic side effects. The present study was done to predict the clinical factors for response to letrozole in infertile PCOS patients. A total of 63% of the study population showed successful ovulation with the incremental dose of letrozole from 2.5 mg to 7.5 mg in consecutive cycles in the study. Results were consistent with the study done by Khaliq Showman et al[6] where the ovulation rate in study participants was 64.2% and the pregnancy rate was 32.8%. Thilina Sanjeewa et al[7] also showed a 50 % ovulation rate with letrozole at a dose of 2.5 mg/day.

In this study mean BMI was 28.28 ± 3.8 kg/m$^2$ (no participant was underweight, only 19% had normal BMI rest 81% were overweight or obese). The mean waist circumference was 83.97 ± 7.60 cm. Our study showed that patients with higher waist circumference are more likely to remain anovulatory. Our study results were consistent with the results of Khaliq showman et al[6], in whose study the mean BMI was 27.6 ±3.5 kg /m2 and mean waist circumference was 86.2± 16.4 cm.

As PCOS is often associated with central obesity, concomitant insulin resistance, and hyperinsulinemia, weight reduction and lifestyle modification are considered important in overweight women with PCOS with anovulatory infertility[8]. Weight reduction reduces hyperinsulinemia and insulin resistance and increased physical activity increases insulin sensitivity[9]. This improves the hormonal imbalance in the ovary and reduces androgen dominance[10].

Hirsutism was assessed according to the ferryman-Gallwey (FG) score. A total of 42.9 % of the women in the responder group and 75.7 % in the non-responders' group had hirsutism of varying severity. There was a statistically significant difference in the two groups according to the presence of hirsutism (p-value 0.003). Our results were comparable with the result of Khaliq showman at el[6], where hirsutism was seen in 83.4% of the women and the FG score was 8 to 15. Among the total hirsute women, 78.4 % had mild hirsutism and the remaining 27.6% had moderate to severe hirsutism. In our research, the existence of hirsutism was found to have an adverse prognosis for both ovulation and pregnancy while in a study by Rausch et al[11] presence of hirsutism was noted to have an adverse prognosis on conception, pregnancy, and live births.

In the present study effect of increasing the dose of letrozole on mean endothelial thickness was also noted. Endothelial thickness was significantly more in the ovulatory group as compared to the ovulation failure group (p <0.001). Mean endothelial thickness also increased with an increase in the dose of letrozole. With an increasing dose of letrozole increment in endometrial thickness was found because of increased chances of ovulation. Our results were compared with the results of Ahmed Walid A. Morad et al[12] who observed that the midcycle endometrial thickness is significantly greater in the letrozole cycles compared to the previous CC cycles. Similarly, Nik Hazlina Nik Hussain et al[13] also found in their study that means ET in the Letrozole group was thicker than in the Clomiphene citrate group at mid-cycle.

## CONCLUSION AND RECOMMENDATIONS

Letrozole can be considered as a suitable ovulation induction agent in patients with PCOS induced infertility. Identification of various factors affecting response to letrozole may help the clinician in deciding the most appropriate ovulation induction protocols in PCOS women. Thus, ovulation induction protocol can be individualised based on

certain clinical parameters. A predictive ovulation score can be developed in future from basic clinical parameters. We recommend lower thresholds for switching to alternative options such as gonadotropins in women with PCOS-related infertility, who are obese with features of irregular cycles and clinical hyperandrogenism. This will make ovulation induction more patient-tailored and cost-effective. Moreover, this will help in prognosticating the patients and also save a lot of time thus decreasing total time to pregnancy.

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