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Dr. Ramesh C Patel
Resident, Department of
Obstetrics & Gynecology, GMERS
Medical College, Dharpur, Patan,
Gujarat, India

Dr. Mukund B Patel
Resident, Department of
Obstetrics & Gynecology, GMERS
Medical College, Dharpur, Patan,
Gujarat, India

Evaluation of letrozole in infertile women with polycystic ovarian syndrome

Dr. Ramesh C Patel and Dr. Mukund B Patel

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Abstract

Introduction: Ovulation dysfunction is one of the most common causes (prevalence 30-40%) of infertility. PCOS is one of the common cause of infertility. Letrozole is a potent, non steroidal, aromatase inhibitor which is currently being used as ovulation inducing agent with few side effects. The aim is use of Letrozole as a first line ovulation inducing agent in polycystic ovarian syndrome (PCOS) as an alternative other commonly used ovulation induction agent.

Methods: Total 220 patients of PCOS were included in the study. Diagnosis of PCOS was made on Rotterdam criteria. All patients received 2.5 mg Letrozole daily since day 2-6 of cycle. Human chorionic gonadotrophin was administered at a dose of 5,000 IU when at least 1 mature follicle (17-25mm) was detected. Timed intercourse was advised to the patients after 24-36 hrs of hCG. Then the number of follicles, endometrial thickness, ovulation rate & pregnancy rate were measured.

Results: In this study 95.45% patients ovulated on first cycle, mono follicular development was significant greater in majority (86.4%) and only 2 patients developed mild OHSS, with good endometrial response, majority developed ET > 7.1mm. Out of 220 patients, 42 patients conceived out of which 14 had miscarriage, 10 had ectopic pregnancy.

Conclusion: Letrozole can be used as a first line drug to induce ovulation and pregnancy in PCOS patients.

Keywords: Infertility, PCOS, Letrozole

Introduction

Infertility is a worldwide problem, affecting the total wellbeing of the couples involved. The conflux of personal, interpersonal, social and religious expectations may bring a sense of loss, failure and exclusion to those who are infertile [1]. Living as an involuntarily childless woman is challenging for femininity and female roles in society. Thus it is not just a medical problem but also a social one. It has serious demographic, social and health implications [2].

The number of couples seeking medical help for infertility is increasing dramatically. The incidence of infertility appears to be increasing, its incidence is 5-15%, but varies among any population worldwide with an average of 9% [3]. WHO estimates that 60 to 80 million couples worldwide currently suffer from infertility? It is said to be primary, if the couple have never achieved conception or secondary if there has been previous conception. Incidence of female infertility is 45.67%, male infertility is 54.33% and may be both can get involved in some of the cases, range from region to region [4].

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 [5]. Female factor infertility can be due to multiple causes like ovulatory factor, tubal factor, uterine factor, pelvic factor, decreased ovarian reserve and others. The gynaecologist'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 [6]. The most common initial diagnostic tests for evaluation of an infertile couple are mid-luteal phase progesterone assay, a test for tubal patency, such as hysterosalpingography (HSG) for females and semen analysis for males. Laparoscopy is reserved for further diagnosis or may be used in combination with endoscopic surgery. Frequently, problems that cannot be discovered by an external physical examination or other radiological investigations can be discovered by laparoscopy and hysteroscopy, two procedures that provide a direct look at the pelvic organs Directly [7].

Corresponding Author:
Dr. Ramesh C Patel
Resident, Department of
Obstetrics & Gynecology, GMERS
Medical College, Dharpur, Patan,
Gujarat, India

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 hysterosalpingography. 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 [8, 9].

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. The present study was carried out to evaluate our knowledge in regards to role of letrozole, an upcoming ovulation inducing agent as a safe, effective, cost effective and accurate tool for assessment and planning the protocol for management of infertility. This study will give an opportunity to compare the pathological nature of infertility amongst the female population in the Indian subcontinent.

Materials and Methods

The main source of data for this study are the women with primary and secondary infertility with anovulation attending the department of obstetrics and gynaecology Hospital. Approval for this study protocol and clearance were obtained from the Ethical Review Committee. Present study is the prospective one. Totally, 220 women were included who 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.

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.

The following investigations either alone or in combination were used:

- 1) HSG- In this study generally done after 3 cycles of failed

ovulation induction or if indicated before 3 cycles.

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 47 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 27.85 years and mean age of husbands were 33.23 year. Hence this study shows maximum an ovulatory cycles were common in age group 26.55 + 4.76.

In the present study, out of 220 cases; 174 cases were of primary infertility & 46 patients were of secondary infertility. The majority of cases were facing primary infertility (79.1%) due to PCOS. So, this is of inference that PCOS is a major cause for primary infertility. In our study, majority of patients were overweight (BMI 21-25 were 50.9%, BMI 26-30 were 35.45%) and few were obese. (BMI>30 i.e.4.5%). Hence, our study depicts that PCOS is commonly accompanied by increase in body weight (BMI).

In our study, out of 220 subjects; 132 patients underwent diagnostic hysteroscopy with chromopertubation + ovarian drilling. Out of 132 patients; 28 patients had bulky ovary, 4 patients had uterine anomalies, all the patients had

features of PCOS and 2 patients had right fallopian tube block (table 1).

The study shows that out of 220 patients 4.5% patients developed an average of less than 1 dominant follicle i.e. occasional an ovulatory cycle, 86.4% patients developed an average of 1 dominant follicle i.e. 1 dominant follicle per cycle, & 9.1% patients developed an average of more than 1 follicles i.e. more than 1 dominant follicle in occasional cycle. Hence Tablet letrozole caused mono follicular development in majority of subjects i.e. 86.4% of subjects. In our study out of 220 patients who were induced with letrozole 210 patients achieved ovulation in 1st cycle of treatment. While 10 patients didn't achieve ovulation in 1st cycle of treatment. So, Ovulation during 1st cycle of treatment was 95.45%. In our study, out of 220 patients 42 patients conceived after induction with letrozole. Hence in our study the conception rate was 19.1%. (Table 3).

Table 1: laparoscopic findings

Laprosopic findings		Frequency
Uterus	Normal	128
	Arcuate	2
	Bicomuate	2
	Not done	88
Ovary	B/L PCOS	132
	Bulky	28
	Not done	88
Tubes	Rt. Tube block	2
	Normal	130
	Not done	88

Table 2: average no. of dominant follicles per cycle

Avg. No of dominant follicle	Frequency
0	10
1	190
1.1 – 2	20
Total	220

Table 3: ovulation in 1st cycle of treatment

Ovulation in 1 st cycle of treatment	Frequency
Yes	210
No	10

Discussion

Infertility is seldom, if ever a physically debilitating disease. Till date Clomiphene citrate is still considered drug of choice for ovulation. It has better ovulation rate but, is not equally successful in all situations. Alternative treatments to Clomiphene Citrate with drugs such as letrozole have attracted attention. It is an aromatase inhibitor which used to be primarily considered for women with breast cancer [10]. Recently Letrozole has been increasingly used for ovulation induction because of its less anti-estrogenic & systemic side-effects. This prospective clinical trial aims to see the effect of letrozole on infertile patients with PCOS on basis of multiple factors like monofollicular development, endometrial thickness, and ovulation rate & ultimately its effect on successful pregnancy outcome [11].

Maruf Siddiqui et al [12]. 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 atleast 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.

In our Study mono follicular development was 86% i.e. 190 cases out of 220. And majority of cases this was achieved in 1st cycle of treatment itself. Hence in our study mono follicular development was quite significant. In our study we achieved 95.45% ovulation with Letrozole induction. R.F. CASPER, 2009 [13], in the study compared the use of aromatase inhibitor Letrozole with CC for ovulation induction in patients with PCOS. Two studies were compared in his analysis. He concluded that JetrozoJe is at least as effective as clomiphene for inducing ovulation and achieving pregnancy in patients with PCOS. Potential advantages of letrozole include reduced multiple pregnancies, absence of antiestrogenic adverse effects, and the subsequent need for Jess intensive monitoring.

ATAY et al., [14] 2006 assessed the efficacy of Als for OI 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.

Conclusions

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. Hence, Letrozole can be recommended as drug of choice for patients with an ovulatory infertility.

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