International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Ovulation Induction and Clinical Pregnancy with Letrozole Alone and in Combination with Inj HMG in PCOS Related Infertility Patients: A Prospective Study

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Abstract: ***The aim of study was to compare letrozole alone versus letrozole in combination with HMG for ovulation induction and clinical pregnancy in PCOS Patients. Materials and Methods: A total of 150 consecutive patients were enrolled in the study and were divided into two groups. Group "A"(n=75) received letrozole alone. Group "B"(n=75) received letrozole as well as 75 IU HMG. Transvaginal ultrasound was done for follicular growth monitoring. Ovulation was triggered by an intramuscular injection of 5,000-10,000 U of human chorionic gonadotropin (HCG). On the same day LH, E2 and progestrone levels were measured. Signs of Ovulation were confirmed by TVS. After treatment, the clinical pregnancy (including normal pregnancy and abortion), multiple pregnancy and average medication cycle of clinically pregnant patients of the two groups were compared. Results: Both the groups received treatment of ovulation induction for 4 to 6 cycles or till pregnancy was confirmed, which ever one was earlier . The pregnancy rate of the Group B was 54.7 %, which was significantly higher than that of the Group A (29.3 %). This difference was statistically significant (P<0.05). Conclusion: Letrozole in combination with low-dose HMG on alternate days shows good results in PCOS related infertility patients and had a satisfactory effect on ovulation and high clinical pregnancy rate in these patients.***

1. Introduction

Infertility is defined as the inability to conceive naturally after one year of regular unprotected intercourse. The chance to conceive depends on the length of sexual exposure, frequency of coitus, and couple's age[1,2]. Both males and females are equally responsible for the causes[2]. Most of the infertile couples have one of these three major causes including a male factor, ovulatory dysfunction, or tubal-peritoneal disease[3].

Polycystic ovarian Syndrome (PCOS) can lead to anovulatory infertility because of an increased amount of testosterone and LH and decrease uptake of glucose by muscle, fat and liver cells resulting in the production of large amounts of insulin by the pancreas. Low FSH levels also hinder the production of eggs from the ovarian follicles, and lead to form fluid-filled ovarian cysts that eventually cover the whole ovary and prevent conception[4].

PCOS is a heterogeneous disorder that is defined by a combination of signs and symptoms of androgen excess (hirsutism and/or hyperandrogenaemia) and ovarian dysfunction (oligo-ovulation and/or polycystic ovarian morphology (PCOM)), provided that other specific diagnoses, such as hyperprolactinaemia and non-classic congenital adrenal hyperplasia, have been excluded. The prevalence of PCOS in premenopausal women ranges from ~6% (using the older, more restrictive criteria) to ~20% (when applying current, more inclusive definitions)[2–5], possibly making this syndrome the most common endocrine and metabolic disorder in women of reproductive age. The condition occurs in about 5% to 10 % of women accounting for 30% to 60% of anovulatory infertility[6]. There is a spectacular increase in the prevalence of PCOS all over the world especially in Asia. The condition seems to be on a rise in Kashmir valley although systematic studies on the subject are still underway[7]. Incidence of PCOS is 8 to 20% worldwide and in India it ranges from 2.2 to 26%[8].

Three definitions for PCOS remain valid at present. Three definitions for PCOS remain valid at present[10, 11, 12].

Criteria for Diagnosis of Polycystic Ovary Syndrome (Other Hormonal and Androgen Excess Condition Being PreviouslyExcluded)

NIH/NICHD (must meet both criteria)				ESHRE/ASRM (Rotterdam Criteria - 2004)				Androgen Excess Society – 2006			
Includes Following	All	of	the	Includes following	two	Of	The	Includes following	All	of	the
Clinical	and	/	or	Clinical	and	/	Or	Clinical	and	/	or
biochemical				biochemical				Biochemical			

hyperandrogenism				Hyperandrogenism					hyperandrogenism						
Menstrual				Oligo-ovulation				Or	Ovary dysfunction and						
dysfunctional				annovulation					/ or polycystic ovaries						
				Polycystic ovaries											

ESHRE/ASRM = European Society for Human Reproduction and Embryology /American Society for Reproductive Medicine;
NIH/NICH = National Institute of Health / National Institute of Child Health and Human Disease.

The Rotterdam definition is the most widely used PCOS classification, and it is currently supported by most scientific societies and health authorities[9,13-16.]. The most severe clinical manifestation is the classic PCOS phenotype that presents with both hyperandrogenism and oligo-ovulation, irrespective of the presence of PCOM. The next most severe phenotype is ovulatory PCOS (presents with hyperandrogenism and PCOM), and the non-hyperandrogenic phenotype, which consists of oligo-ovulation and PCOM, is the least severe phenotype[17]. The latter category is not considered PCOS by the AE–PCOS statement[1]. Similarly, PCOS is a heterogeneous disorder in terms of its link with insulin resistance and metabolic dysfunction. This association is much stronger in women with the classic PCOS phenotype than in those with ovulatory PCOSor in those with the non-hyperandrogenic phenotype[10.] .

PCOS is a complex disease, and treatment should include interventions to address the problems of infertility, hyperandrogenism, obesity, insulin resistance, and other features[18]. Often a single intervention may not address this issue, and a combination of two may have a beneficial effect. The treatment options for infertility include:

- Lifestyle modification (diet and exercise)
- Ovulation induction (clomiphene citrate [CC] and letrozole)
- Surgical - Laparoscopic ovarian drilling (LOD)
- Ovulation induction with homologous intrauterine insemination (IUI)
- *In vitro* fertilization (IVF).

Obesity is associated with irregular menstrual cycles. Abdominal obesity, in particular, has been shown to cause failure to respond or delayed response to ovulation induction medications and surgical interventions, in women with PCOS. Weight loss through lifestyle modifications in diet and exercise is therefore recommended as:

The European Society of Human Reproduction and Embryology (ESHRE) recommends a low-calorie diet (1000-1200 kcalwith a decreased glycemic load or any calorie restricted diet to achieve 5% weight loss. Atkins' diet which comprises a verylow-calorie diet has shown to cause significant weight loss in PCOS (12% in 24 weeks) and improves reproductive outcome[18].

Current American Society for Reproductive Medicine (ASRM) recommendations for lifestyle modification in obesity include:

- Weight loss of 7% of body weight
- Increased physical activity to at least 150 min weekly of moderate activity such as walking.

Letrozole is a triazole (antifungal) derivative that is a reversible, competitive aromatase inhibitor and at the usual doses used for breast cancer (2.5 mg/d), inhibits estrogen levels by up to 99%.Inhibition of aromatization blocks both circulating estrogen (produced from ovarian follicles and from peripheral conversion of androgens) and locally produced estrogen in the brain to release the hypothalamic/pituitary axis from estrogenic negative feedback. The resultant increase in gonadotropin secretion would stimulate growth of ovarian follicles similar to the effect of CC. Owing to the short half-life (approximately 45 h) letrozole would be ideal for ovulation induction as it would be cleared rapidly. As aromatase inhibitors do not deplete ERs, normal negative feedback mechanisms for FSH in the brain remain intact. As the dominant follicle grows and estrogen levels rise, normal suppression of FSH and atresia of the smaller growing follicles occur. It is likely that the optimal daily dose of letrozole for a 5-day course of treatment is between 2.5 and 5.0 mg. Doses higher than 5 mg per day for 5 days could result in persistence of aromatase inhibition and estrogen levels too low for normal endometrial development by the time of ovulation[18,19].

The main side effects of letrozole when used long term for treating breast cancer include mild gastrointestinal disturbances, hot flushes, headache, and back pain. These side effects, with the exception of occasional mild headaches, have not been observed by us when using letrozole for only 5 days[18,19].

The use of gonadotropins[20] dates back to 1961. They are derivatives of urinary products but recently gonadotropins have been manufactured using recombinant technology. Both types have similar ovulation and pregnancy rates. Gonadotropins developed from recombinant techniques are more patient friendly as they can be given subcutaneously; however, they are expensive when compared to those derived from urinary products which are given intramuscularly. The prerequisites for gonadotropin therapy are exclusion of uterine cavity abnormalities (myomas/adhesions), tubal obstruction and advanced endometriosis, pelvic adhesion, and poor semen quality.

2. Methods

The study was conducted in the Department of Obstetrics and GynaecologyatLalla Ded Hospital, GMC Srinagar, a tertiary care centre over a period of 18 months. It was a prospective observational study. Ethical clearance was obtained from the institutional ethical committee of the medical college. Written informed consent was obtained from all the participants of the study after explaining the risks and benefits of the planned treatment.

Inclusion Criteria:

1) Patients with age 20-35 years
2) Patients with infertility lasting more than 1 year
3) Male partner having semen analysis according to WHO 2010
4) Normal hysterosalpingography (HSG) or laparoscopy
5) Clomiphene resistant cases of PCOS
6) Normal hormone (e.g. FSH, LH, estradiol (E2), testosterone (T), insulin and prolactin) levels in the venous blood of all patients detected on the 2nd-4th days of menstruation.

Exclusion Criteria:

1) Patients having history of ovarian surgery or complication with endometriosis or pelvic adhesions
2) Patients complicated with liver, kidney and thyroid dysfunction
3) The presence of any infertility factor other than anovulatory PCOS such as hyper-prolactinemia, hypothyroidism hypothalamic amenorrhea, premature ovarian failure and ovarian tumor.

All patient were diagnosed as PCOS according to the 2003 Rotterdam criteria[7], i.e. two of the following three criteria were met:

1) Oligo/Anovulation.
2) Hyperandrogenism.
   - Clinical (hirsutism or less commonly male pattern alopecia) or
   - Biochemical (raised FAI or free testosterone)
3) Polycystic ovaries on ultrasound.

Demographic details namely age, duration of marriage, years of infertility and baseline serum levels of TSH, FSH, LH and prolactin were noted.

A total of 150 consecutive patients were enrolled in the study and were randomly divided into two groups of 75 each. Group "A" received letrozole in a dose of 2.5 mg to 5mg orally on 3rd to 5th day of menstrual cycle for 5 consecutive days. Group "B" received letrozole in a dose of 2.5 to 5 mg/day on the 3rd to 5th day of menstrual cycle for 5 consecutive days and starting from the day of oral administration of letrozole, 75 IU HMG was injected intramuscularly on alternate days for 5 consecutive doses. Ovulation induction was started after baseline sonography on 3rd day of menstruation

Starting from the 10th day of menstruation, the growth conditions of follicles and endometrium in the patients were monitored once every other day by transvaginal ultrasound, and then daily when the average diameter of the follicles was ≥16mm. The day when the size of at least one dominant follicle reached 18mm, ovulation was triggered by an intramuscular injection of 5,000-10,000 U of human chorionic gonadotropin (HCG). On the same day, the venous blood of patients was drawn to examine the LH, E2 andprogestronelevels, patients were advised to have sexual intercourse on alternate days from day of periods. Ovulation was expected after 36hrs of injection HCG, and it was confirmed by TVS. Crenation of the follicle and appearance of fluid in the pouch of Douglas were considered to be the signs of rupture of follicle. The only method for ultrasonography used was transvaginal, and it was done by the same operator/observer, using the same ultrasound equipment throughout the study.

***Observation indices*:**

The numbers of completed cycle, ovulated cycle and single follicle-ovulated cycle in the two groups were recorded during ovulation induction, and the endometrium, follicle as well as reproductive hormone levels were observed on HCG injection day. In addition, record was made of OHSS in both groups. After treatment, the clinical pregnancy (including normal pregnancy and abortion), multiple pregnancy and average medication cycle of clinically pregnant patients of the two groups were compared.

3. Observations & Results

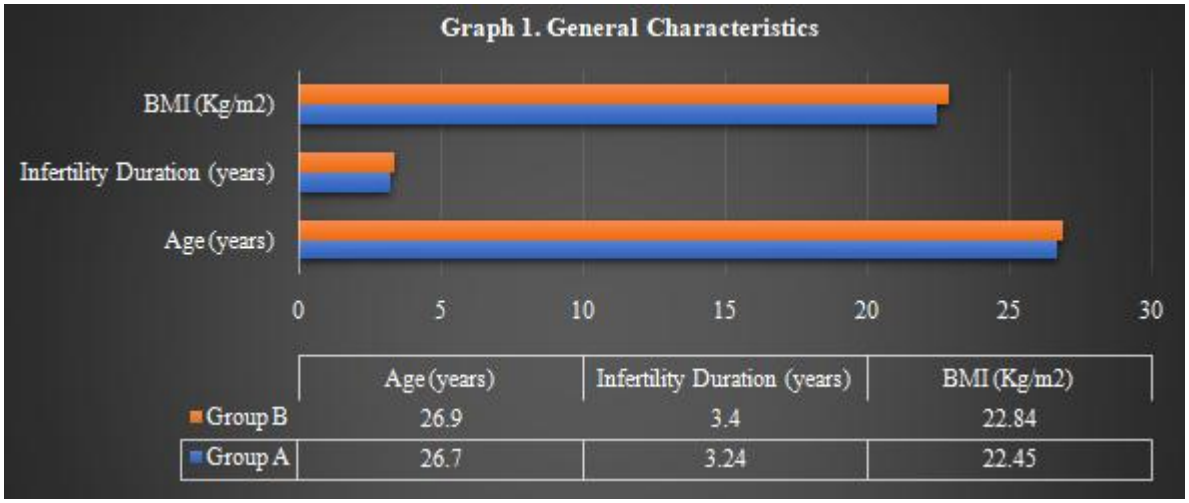
Table 1 depicting the general characteristics of Group A and Group B.

Table 1: General Characteristics (Mean ± SD)

Group	No. of patients(n)	Age (years)	Infertility Duration (years)	BMI (Kg/m^2)
Group A	75	26.7 ± 2.2	3.24 ± 1.0	22.45 ± 1.7
Group B	75	26.9 ± 2.2	3.4 ± 1.0	22.84 ± 1.7
p-value	-	> 0.05	> 0.05	> 0.05

Group A---Letrozole Group; Group B—Letrozole +HMG group

Evaluation of the baseline characteristics of the groups showed that there were no significant differences in age (p >0.05), infertility time (p >0.05) or body mass index (p >0.05).



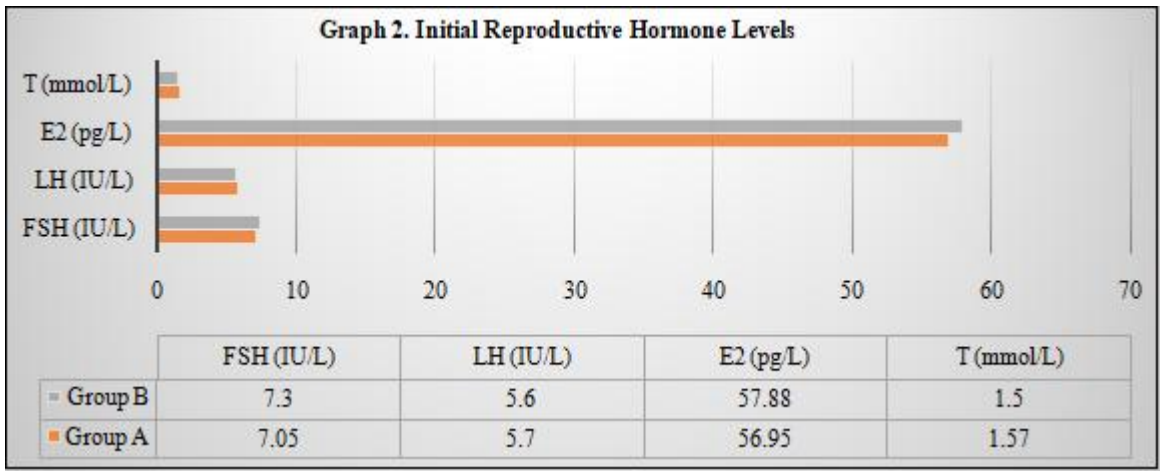
Graph 1: General characteristics of Group A and Group B

Table 2: Initial Reproductive Hormone Levels

Group	No. of patients(n)	FSH (IU/L)	LH (IU/L)	E2 (pg/L)	T (mmol/L)
Group A	75	7.05 ± 1.5	5.7 ± 0.8	56.95 ± 8	1.50 ± 0.5
Group B	75	7.3 ± 1.4	5.6 ± 0.8	57.88 ± 8	1.57 ± 0.5
p-value	-	> 0.05	> 0.05	> 0.05	> 0.05

E2—Estradiol; T—Testosterone

Table 2 depicts the Initial reproductive hormone levels in both groups. Moreover, the base serum hormone levels (luteinizing hormone, FSH, E2 and testosterone) were not significantly different between the 2 groups either. The respective P values for all the parameters were more than 0.05 indicating that the differences were not statistically significant.



Graph 2: Comparison of Initial reproductive hormone levels in both groups

Table 3: Ovulation induction cycles

Group	No. of patients (n)	Completed Cycle	Ovulated Cycle (%)	Single follicle ovulation cycle
Group A	75	310	157 (52.3%)	75
Group B	75	258	168 (65.1 %)	110
p-value	-	-	<0.001	-

Table 3 represents Ovulation induction cycles. The Group A (LE group) had the most completed cycle (310 cycles), 157 (52.3%) of which had ovulation. The Group B (LE + HMG) group completed the fewest cycles (258 cycles), with 168 (65.1%) of them ovulating. This difference was statistically significant (P<0.05) (Table 3 and Graph 3). Graph 3 represents Ovulation induction cycles.

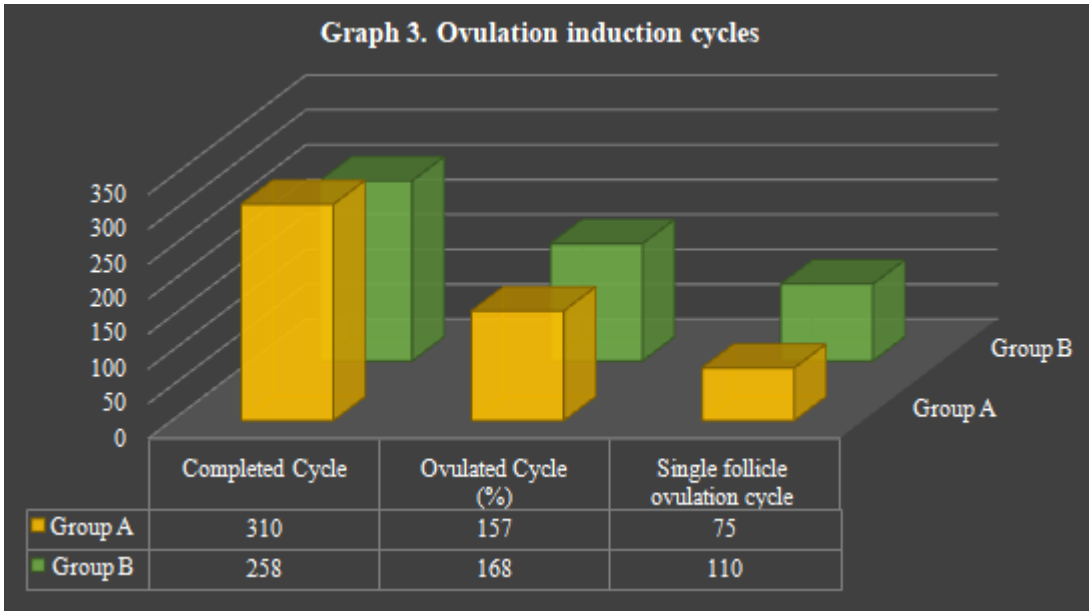
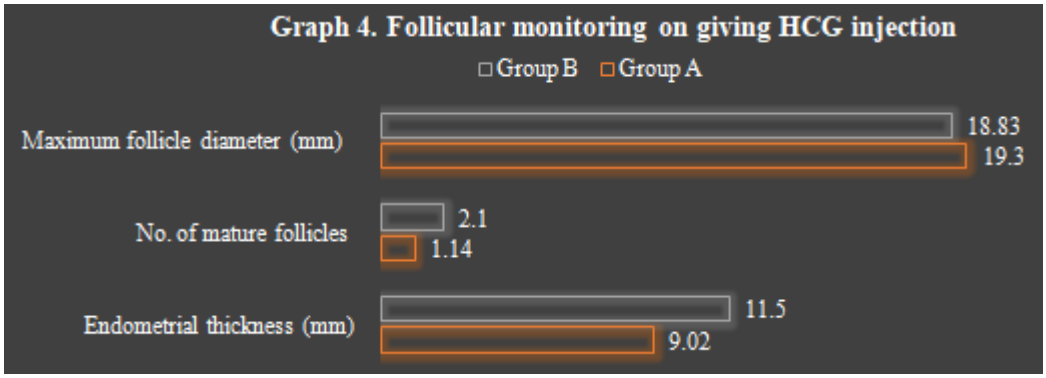


Table 4: Follicular monitoring on giving HCG injection

Group	No. of patients (n)	Endometrial thickness (mm)	No. of mature follicles	Maximum follicle diameter (mm)	OHSS (Case)
Group A	75	9.02 ± 0.66	1.14 ± 0.8	19.3 ± 1.2	2
Group B	75	11.5 ± 1.2	2.1 ± 1.3	18.83 ± 1.17	4
p-value	-	< 0.001	< 0.001	> 0.05	> 0.05

Table 4 shows on HCG injection day, both the endometrial thickness (11.5 ± 1.2) and number of mature follicles (2.1 ± 1.3) of the Group B were significantly higher than those of Group A (P<0.001), but the follicle diameters were similar (P>0.05). Patients from both the groups suffered from OHSS, but the difference was not statistically significant (P>0.05), though the incidence was higher in gonadotropin + letrozole group.

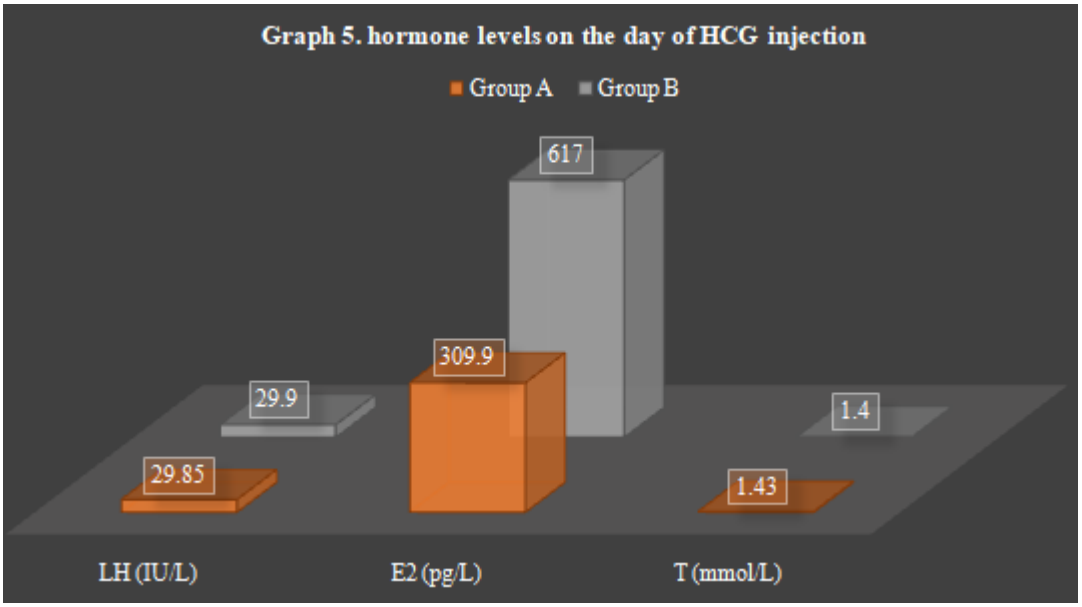


Graph 4: Shows follicular monitoring on giving HCG injection

Table 5: Hormone levels on the day of HCG injection (Mean ±SD)
E-EstradiolT -testosterone

Group	No. of patients(n)	LH (IU/L)	E2 (pg/L)	T (mmol/L)
Group A	75	29.85 ± 5.7	309.9 ± 75.4	1.43 ± 0.5
Group B	75	29.9 ± 5.8	617 ± 84.4	1.40 ± 0.5
p-value	-	> 0.05	< 0.001	> 0.05

Table 5 shows Hormone levels on HCG injection day. On the day of HCG injection, E2 levels were significantly higher in group B while as LH and T levels were comparable.

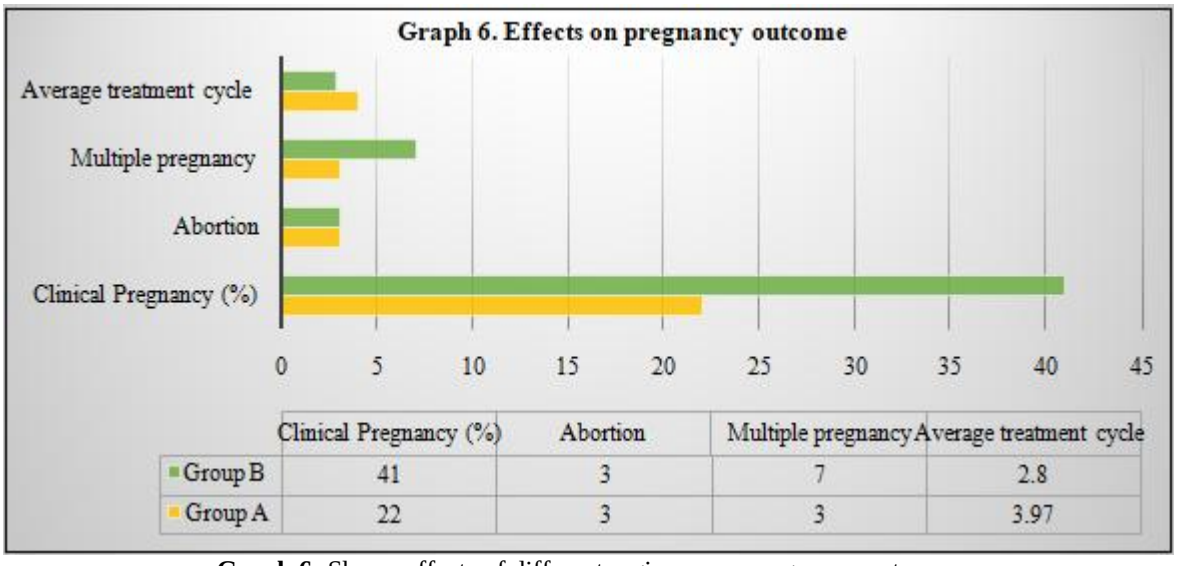


Graph 5 shows Hormone levels on the day of HCG injection

Table 6: Effects of different regimens on pregnancy outcome

Group	No. of patients (n)	Clinical Pregnancy (%)	Abortion	Multiple pregnancy	Average treatment cycle
Group A	75	22	3	3	3.97 ± 0.9
Group B	75	41	3	7	2.8 ± 1
p-value	-	<0.05		-	> 0.05

Table 6 shows effects of different regimens on pregnancy. The pregnancy rate of the Group B was 54.7 %, which was significantly higher than that of the Group A (29.3 %) (P<0.05). There were no statistically significant differences in the abortion rate and multiple pregnancy rate between the groups (P>0.05). The average treatment to pregnancy of the Group B group was significantly shorter than that of the Group A (P<0.05), which was statistically significant.



Graph 6: Shows effects of different regimens on pregnancy outcome

4. Discussion

In this study, the mean age at presentation for Group A and Group B was 26.7 (± 2.2) years and 26.9 (± 2.2) years respectively.

In current study, the mean BMI at presentation for Group A and Group B was 22.45 (± 1.7) kg/m^2 and 22.84 (± 1.7) kg/m^2 respectively.

In this study, the Group A (LE group) had 52.3% ovulation while as group B (LE + HMG) group had 65.1% ovulation which was statistically significant (P<0.05)also the pregnancy of group B was 54.74% which was significantly higher than that of group A (29.3%) (P<0.05)

Badawy *et al.*[24] reported a pregnancy rate of 23.7% with the letrozole + gonadotropin group. **Badawy *et al.*[24]** reported a pregnancy rate of 23.7% with the letrozole + gonadotropin group. **Jee *et al.*[25]** reported pregnancy rates for

letrozole to be 18.2% in combination with gonadotropins in their prospective pilot study.**The pregnancy rates observed in both the abovementioned studies were lower than those observed in our study.*This may be attributed to the different dose of gonadotropin used in these studies.***

In our study, the maximum follicular size on the trigger day in group A was 19.3 ± 1.2 mm while in group B, it was 18.83 ± 1.17 mm, the difference between the two groups being statistically insignificant. However, the number of mature follicles per cycle was higher in group B (2.1 ± 1.3) as compared to group A (1.14 ± 0.8), the difference between the two being highly significant statistically (*P* value < 0.001). **Badawy *et al.*[24]**, observed the follicle number being 2.6± 0.43 in the letrozole group in their study. **Jee *et al.*[25]** reported similar findings in their study with significantly lesser number of follicles observed in the letrozole group (3.2 ± 1.7 vs. 5.6 ± 2.4). **.In another study by Jee et al.[25]**, the mean number of dominant follicles in the letrozole +hMG group were 3.2 ± 1.7.

In the present study, the mean endometrial thickness was greater in Group B (11.5 ± 1.2 mm) than in Group A (9.02 ± 0.66), the difference being statistically significant (P value < 0.001), which was in agreement with ***Malhotra et al.*[84]** whose study also gave a conclusion that better number of follicles and improved ET result in higher pregnancy rate in letrozole-human menopausal gonadotropin (HMG) protocol in comparison to letrozole alone protocol. In the present study, the mean endometrial thickness was greater in Group B (11.5 ± 1.2 mm) than in Group A (9.02 ± 0.66), the difference being statistically significant (*P* value < 0.001), which was in agreement with **Malhotra *et al.*[26] whose study also gave** a conclusion that better number of follicles and improved ET result in higher pregnancy rate in letrozole-human menopausal gonadotropin (HMG) protocol in comparison to letrozole alone protocol. **Bu Fang XU[23]** did not find statistically significant difference between endometrial thickness between the two groups.

There were no statistically significant differences in the abortion rate and multiple pregnancy rate between the groups (P>0.05). All the abortions in both the groups were early abortions, which may be due to poor endometrial receptivity or some genetic factor. In the present study, there was one ectopic pregnancy in the Group B. The patient with ectopic pregnancy had a history of ectopic pregnancy in the past, which may be a risk for recurrence of ectopic pregnancy.

In our study, multiple pregnancies observed in Group A and Group B were 3 and 7 respectively, This may be attributed to the low-dose gonadotropins used in Group B. Both the groups in this study suffered from OHSS, but the incidence rates were similar. It is well-documented that single-use or high-dose HMG may lead to multiple pregnancy and OHSS, so it is recommended to minimize the dosage of HMG[21,22].

5. Conclusion

In conclusion, the regimen using LE in combination with low-dose HMG on alternate days had a satisfactory effect on ovulation and endometrium , and high clinical pregnancy rate, which provides a promising option for the treatment of patients with PCOS related infertility.

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