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A comparative study to evaluate the role of Letrozole and low dose human menopausal gonadotrophin on ovulation induction in polycystic ovarian syndrome patients

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Abstract--Background: Polycystic ovarian syndrome (PCOS) is a multifaceted syndrome that affects multiple organ systems with significant metabolic and reproductive manifestations. Treatment must be individualized on the basis of patient's presentation, and desire for the pregnancy. Objective: To study the role of letrozole (LE) and low dose human menopausal gonadotrophin (HMG) on ovulation induction in the polycystic ovarian syndrome patients. Material & Methods: The present hospital based double blind clinical trial, recruited total 105 patients' of age 21 to 35 years women with PCOS among those attending the gynecology outpatient's clinic in Hind Institute of Medical Sciences Safedabad Barabanki in the period from Sept 2018 to Sept 2021 were enrolled. Observation: Endometrial thickness, and number of the mature follicles of the LE+HMG group were higher significantly than other two groups ($P < 0.001$). Effects of

different regimens on pregnancy. Pregnancy rate of LE+HMG group was 54.3%, which was insignificantly higher than LE group (31.4%) and HMG group (34.3%) ($P>0.05$). There were also no statistically significant differences in rate of abortion, and rates of multiple pregnancy among the three groups. All the three groups suffered from OHSS, but the incidences rates were comparable. Conclusion: The PCOS infertility by using regimen LE in combination with the low dose intra-muscular injection of HMG has adequate therapeutic properties on ovulation induction, less medication cycle and great clinical pregnancy-rate, which is hopeful for management of patients having PCOS infertility.

Keywords--polycystic ovarian syndrome, human menopausal gonadotropin, letrozole, ovulation, pregnancy.

Introduction

Polycystic ovary syndrome (PCOS) is commonest endocrinopathy in the reproductive age women with estimated prevalence of 8.0–13.0%. Its pathogenesis comprises insulin resistance, and hyper androgenism which drive reproductive (menstrual dysfunction, and infertility), metabolic (diabetes, metabolic syndrome, and cardiovascular risk-factors) and psychological (depression, anxiety, and degraded quality of life) complications. Given high occurrence, and assorted features across life-span, in addition to high prevalence of obesity that further worsens its clinical features, the PCOS contributes to global burden of disease. It is hence imperative to recognize condition early to enable interventions, and prevent complications. The diagnosis of PCOS is based on the oligo-anovulation (OA), biochemical, or clinical hyperandrogenism (HA) and the polycystic ovary morphology (PCOM) on the ultrasound extending across original 1990 National Institutes of Health (NIH) criteria (OA, and HA), 2003 Rotterdam criteria (any two of HA, OA and PCOM), and Androgen Excess, and Polycystic Ovary Syndrome (AE-PCOS) Society criteria (HA, and OA or PCOM or both).

PCOS is a multi-faceted syndrome which affects multi-pleorgan systems with a significant metabolic, and reproductive manifestations. Treatment must be individualized on the behalf of patient's presentation, and desire for pregnancy. Devices (Levonorgestrel releasing intra-uterine system (Mirena), and Hormonal contraceptives (e.g., patch, pill, vaginal ring)) and medications (Clomiphene, Letrozole, Metformin, Eflornithine (Vaniqa), Finasteride (Proscar), Flutamide, and Spironolactone) used to treat manifestations of PCOS. In recent years, Aromatase inhibitors (AIs), such as letrozole or anastrozole, have been introduced for treatment of the PCOS women with clomiphene citrate (CC) resistant anovulation. It's been assumed that blocking the estrogen production by preventing aromatization in ovary would release hypothalamic pituitary axis from the estrogenic negative feedback.

As a result, the FSH secretion increases; stimulating development of ovarian follicles, though the reducing gonadotropin induced ovulation complication. Human menopausal gonadotropin (HMG), that covers follicle stimulating hormone

(FSH), and luteinizing hormone (LH) could secrete gonadotropin to stimulate follicle maturation, consequently as to stimulate ovulation, and to accelerate development of corpus luteum. Preliminary studies reported that the aromatase inhibitors, and HMG were beneficial for inducing ovulation, and in superovulation. **Error! Bookmark not defined.** By far, there have been no such studies comparing effects of letrozole, and HMG in treatment of the patients having polycysticovary syndrome (PCOS) resistant to the clomiphene citrate. The present hospital-based study aimed the role of letrozole and low dose human menopausal gonadotrophin on ovulation induction in PCOS patients.

Material and Methods

This present hospital based double blind clinical trial, recruited total 105 patients' of age 21 to 35 years women with PCOS among the patients attending gynecology outpatient's clinic in Hind Institute of Medical Sciences Safedabad Barabanki in period from Sept 2018 to Sept 2021 were enrolled in the present study. Diagnosis of the PCOS is based on revised 2003 consensus of Rotterdam criteria at least 2 of following three were met:

- Oligo-ovulation or anovulation
- Hyper-androgenism, clinical or biological
- Polycystic ovaries

Age <21 years and >35 years, Infertility patients caused by non-PCOS ovulatory disorder, or other factors; Patients with previous history of sensitivity to drug (LH or HMG) and Patients who didn't receive treatment after registration according to established regimen, or gave up in midst of treatment were excluded from the study. 100 patients that met the entry criteria were separated in two groups rendering to the received stimulation protocol:

- **LE group:** comprised 35 patients who received Letrozole 2.5 mg daily starting from day 3rd through day 7th of the menstrual cycle for 5 consecutive days.
- **HMG group:** patients comprised 35 women who received intra-muscular injection of the human menopausal gonadotrophin (HMG) dose regimen starting from day 3rd to 7th days of menstrual cycle for five consecutive days.
- **LE + HMG group:** patients comprised 35 women who received orally took 2.5-5.0mg/d-1 LE on 3rd to 7th days of the menstrual cycle for five consecutive days. Starting from the day of 75 IU HMG was intramuscularly injected every other day for five consecutive days.

Primary outcome measures have number of growing, and mature follicles, serum P (ng/ml), serum E2 (pg/ml), and the endometrial thickness (mm). Occurrence of pregnancy, the ovarian hyperstimulation syndrome (OHSS), and miscarriage was noted as a secondary outcome measures.

Statistical Analysis

SPSS 23.0 software (SPSS Inc. Chicago, IL) was used for statistical analysis. Numerical variables were reported as the mean \pm standard Deviation, and

qualitative variables were analyzed using chi square test. Student's t-test or one way ANOVA test was used to analyze quantitative variables. Differences between groups were assessed with Chi-square or fisher's exact test for categorical variables. Two tailed p-values below 0.05 were considered significant ($p < 0.05$).

Observation and Results

No statistical significant differences were seen between the groups regarding body weight, height, age, body mass index (BMI) or Prolactin, E2 and LH (Table No. 1). Clinical presenting signs and symptoms were also comparable between among groups (Table No. 2). After the treatment of PCOS the endometrial thickness and number of the mature follicles of LE + HMG group were higher significantly than other two groups ($P < 0.001$). Effects of the different regimens on the hormone levels after treatment Prolactin, LH, and E2 levels increased significantly, and there were significant inter-group differences between LH and E2 and prolactin levels. The LE + HMG group had significantly higher prolactin, LH and E2 levels than those of LE and HMG groups ($P < 0.05$) (Table No. 3). Effects of various regimens on pregnancy: The pregnancy rate of LE + HMG group was 54.3%, which was higher insignificantly than that of LE group (31.4%) and HMG group (34.3%) ($P > 0.05$). There were also no statistically significant differences in abortion-rate and multiple pregnancy-rate among the three groups ($P > 0.05$). All three groups suffered from OHSS, but the incidences rates were comparable ($P > 0.05$) (Table No. 4).

Discussion

Polycystic ovary syndrome (PCOS), as one of the commonest endocrine disorders for the childbearing age women, has the incidence rates of 5%-10%, accounting for 30.0%-60.0% of an-ovulatory infertility. Though, it remains very difficult to design proper regimen for ovulation induction of the PCOS patients. PCOS disease among women, characterized by follicle developmental disorders, androgen excess and insulin resistance. For ovulation disorders caused by PCOS, CC, LE and HMG are used currently for ovulation induction. At present, the CC remains first-line drug for an ovulation induction with rates of ovulation as 75.0% to 80.0%, but in recent studies a considerable proportion of the patients didn't get the desirable pregnancy results after CC treatment. In the normal ovulation process, estrogen and progesterone play obvious regulatory roles, and CC has anti-estrogenic effects, but its exact mechanism has not been fully clarified yet. So, present study was conducted to find Role of Letrozole and low dose human menopausal gonadotrophen on ovulation induction in PCOS patients.

No statistical significant differences was seen between the groups regarding body weight, height, age, body mass index (BMI), or Prolactin, E2 and LH (Table No. 1). Clinical presenting signs and symptoms were also comparable between among groups (Table No. 2). Our findings were comparable to Chen Z et al, **Error! Bookmark not defined.** Giuseppe D'Amato and Hager M et al study. Available evidence suggests a dose-response with letrozole, with higher doses producing more mature follicles and higher ovulation rates. Data derived from these patients suggested substantial inhibition of estradiol formation with doses of 2.5–5 mg daily. However, the application of these data to short-term use of the drug in

reproductive age women is highly questionable. Nevertheless, clinical investigation of the drug in infertile women has been generally limited to 5 days of treatment at doses of 2.5–7.5mg daily. The dose has varied from 2.5 being lowest to 7.5 mg being highest, and a single study has been also conducted on a single dose of 20 mg. In this study LE group patients comprised who received Letrozole 2.5 mg daily starting from day 3rd through day 7th of the menstrual cycle for 5 consecutive days and LE + HMG group women comprised who received orally took 2.5-5.0 mg/d-1 LE on the 3rd to 7th days of menstrual cycle for five consecutive days. Starting from day of 75IU HMG was intra-muscularly given every other day for 5 consecutive days.

After treatment of PCOS, endometrial thickness, and number of the mature follicles of the LE + HMG group were higher significantly than other two groups ($P < 0.001$). Effects of the different regimens on the hormone levels after treatment Prolactin, LH, and E2 levels increased significantly, and there were significant inter-group differences between prolactin, LH, and E2 levels. The LE + HMG group had significantly higher prolactin, LH and E2 levels than those of LE and HMG groups ($P < 0.05$) (Table No. 3). Palihawadana TS et al reported small impact of the LE on estrogen or progesterone ratio is favorable to maturation of endometrium, and receptivity increase. Chen Z et al **Error! Bookmark not defined.** study reported that in cycle with the ovulation induction, LE group had somewhat fewer ovulation cycles, and the mature follicles than CC group. E2 hormone level of CC group was somewhat higher and endometrium was thinner than LE group.

As gene product of CYP19, aromatase could act on androstenedione generated from adrenal cortex of the adipose tissues to form estrone, and testosterone in the ovarian tissues to yield androstenedione and then transform the part of androstenedione in estrone. Theoretically, LE might be superior to the CC as it has no peripheral anti-estrogen effect. Our study noted pregnancy rate of the LE+HMG group was 54.3%, which was higher insignificantly than LE group (31.4%) and HMG group (34.3%). There were also no statistically insignificant differences in abortion-rate and multiple pregnancy rates among the three groups. All the three groups suffered from OHSS, but the incidences rates were comparable (Table No. 4). Chen Z et al reported the OHSS incidence rate was also higher slightly than LE group, but the clinical pregnancy rates of two groups were similar. Moreover, two groups had similar completed cycles, and cycles from the treatment to a clinical pregnancy.

Two schedules using HMG were used currently for the ovulation induction: low dose escalation, and the high dose descending. Current world literature suggested low dose escalation regimen is commonly used, that can reduce incidence rates of OHSS, and the multiple follicles by adjusting HMG dosage accordingly to B ultrasound results. Xi W et al and Yun BH et al well-documented that single use or high dose HMG might lead to the multiple pregnancy, and OHSS, consequently it is suggested to minimize dosage of HMG. Thus we assessed effects of LE in combination of the small dose injection of HMG on ovulation induction of the PCOS patients and found combination regimen had an obvious advantages.

Limitation

One limitation of our current study is small number of the enrolled patients that is explained by our choice of strict inclusion/exclusion criteria and single center study. On the other limitation, although present results are promising, and limited by the hospital based double blind clinical trial, particularly, observation period was small. These understandings prompted need for the larger, cohort perspective study to assess efficacy of letrozole, and human menopausal gonadotropin (HMG) in treatment of the patients with PCOS.

Conclusion

Our result suggested that regimen consuming LE in combination with a low dose injection of HMG every next day had the satisfactory effect on the ovulation, short medication cycle, and the high clinical pregnancy rate that provides promising option for treatment of the patients having PCOS infertility. Need of large sample size, and multicenter research is obligatory to confirm application value of regimen in the patients having ovulatory disorder infertility.

References

- Bacci M, Giannoni E, Fearn A, Ribas R, Gao Q, Taddei ML, et al. miR-155 drives metabolic reprogramming of ER+ breast cancer cells following long-term estrogen deprivation and predicts clinical response to aromatase inhibitors. *Cancer Res.* 2016; 76(6):1615-1626.
- Bo HY, Chon SJ, Park JH, et al. Minimal stimulation using gonadotropin combined with clomiphene citrate or letrozole for intrauterine insemination. *Yonsei Med J* 2015; 56:490–6.
- Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod.* 2016; 31(12):2841–55.
- Budinetz TH, Benadiva CA, Griffin DW, Engmann LL, Nulsen JC, DiLuigi AJ. Ovulation rate and cycle characteristics in a subsequent clomiphene citrate cycle after stair-step protocol. *FertilSteril.* 2015; 103(3):675-679.
- Chen Z, Zhang M, Qiao Y, Yang J. Effects of letrozole in combination with low-dose intramuscular injection of human menopausal gonadotropin on ovulation and pregnancy of 156 patients with polycystic ovary syndrome. *Pak J Med Sci.* 2016; 32(6):1434-1438.
- D'Amato G, Caringella AM, Stanziano A, Cantatore C, Palini S and Caroppo E. Mild ovarian stimulation with letrozole plus fixed dose human menopausal gonadotropin prior to IVF/ICSI for infertile non-obese women with polycystic ovarian syndrome being pre-treated with metformin: a pilot study. *Reproductive Biology and Endocrinology* 2018; 16:89.
- Denny L, Bhatla N. Preface for Best Practice and Research Clinical Obstetrics and Gynaecology - issue 29.6. *Best Pract Res Clin Obstet Gynaecol.* 2015; 29(6):765-766.
- Ellakwa HE, Sanad ZF, Hamza HA, Emara MA, Elsayed MA. Predictors of patient responses to ovulation induction with clomiphene citrate in patients with

- polycystic ovary syndrome experiencing infertility. *Int J Gynaecol Obstet.* 2016; 133(1):59-63.
- Ghosh D, Lo J, Egbuta C. Recent Progress in the Discovery of Next Generation Inhibitors of Aromatase from the StructureFunction Perspective. *J Med Chem* 2016; 59(11):5131-514
- Hager M, Hörath S, Frigo P, Koch M, Marculescu R and Ot Jt. Changes in serum markers of patients with PCOS during consecutive clomiphene stimulation cycles: a retrospective study. *Journal of Ovarian Research* 2019; 12:91.
- Masroor K and Maheswari B. Effect of three different doses of letrozole in ovulation induction and its effect on gonadotropins dose in unexplained infertility. *International Journal of Clinical Obstetrics and Gynaecology* 2020; 4(4):142-146
- Palihawadana TS, Wijesinghe PS, Seneviratne HR. Factors associated with nonresponse to ovulation induction using letrozole among women with World Health Organization group II anovulation. *J Hum Reprod Sci.* 2015; 8(2):75-79.
- Shi S, Hong T, Jiang F, Zhuang Y, Chen L, Huang X. Letrozole and human menopausal gonadotropin for ovulation induction in clomiphene resistance polycystic ovary syndrome patients: A randomized controlled study. *Medicine* 2020; 99:4(e18383).
- Sorouri Z, Sharami SH, Tahersima Z, Salamat F. Comparison between unilateral and bilateral ovarian drilling in clomiphene citrate resistance polycystic ovary syndrome patients: A randomized clinical trial of efficacy. *Int J FertilSteril.* 2015; 9(1):9-16.
- Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2022). Post-pandemic health and its sustainability: Educational situation. *International Journal of Health Sciences*, 6(1), i-v. <https://doi.org/10.53730/ijhs.v6n1.5949>
- Tay CT, Hart RJ, Hickey M, Moran LJ, Earnest A, Doherty DA, et al. Updated adolescent diagnostic criteria for polycystic ovary syndrome: impact on prevalence and longitudinal body mass index trajectories from birth to adulthood. *BMC Medicine* 2020; 18:389.
- Williams T, Mortada R, Porter S. Diagnosis and Treatment of Polycystic Ovary Syndrome. *American Family Physician* July 2016; 94(2):106-113.
- Xi W, Liu S, Mao H, Yang Y, Xue X, Lu X. Use of letrozole and clomiphene citrate combined with gonadotropins in clomiphene-resistant infertile women with polycystic ovary syndrome: a prospective study. *Drug Des Devel Ther.* 2015;9: 6001-6008.
- Xiang X, Shankun L, Yongkang Y, et al. Use of letrozole and clomiphene citrate combined with gonadotropins in clomiphene-resistant infertile women with polycystic ovary syndrome: a prospective study. *Drug Des Dev Therap* 2015; 6001-10.
- Yin Q, Fischer L, Noethling C, Schaefer WR. In vitro assessment of putative antiprogesterin activities of phytochemicals and synthetic UV absorbers in human endometrial Ishikawa cells. *GynecolEndocrinol.* 2015;31(7):578-581.
- Yun BH, Chon SJ, Park JH, Seo SK, Cho S, Choi YS, et al. Minimal stimulation using gonadotropin combined with clomiphene citrate or letrozole for intrauterine insemination. *Yonsei Med J.* 2015; 56(2):490-496
- Zhihua C, Mengzhen Z, Yuhuan Q, et al. Effects of letrozole in combination with low-dose intramuscular injection of human menopausal gonadotropin on ovulation and pregnancy of 156 patients with polycystic ovary syndrome. *Pak J Med Sci* 2016; 32:1434-8.

Table 1
Clinical characteristics of the study cases among groups

	Letrozole (n=35)	Human Menopausal Gonadotropin (n=35)	Letrozole + Human Menopausal Gonadotropin (n=35)	F value	P value
Age (Years)	26.77±5.76	27.14±4.39	27.29±4.85	0.097	0.907
Height (cm)	152.57±2.69	152.83±2.95	152.14±2.80	0.529	0.591
Weight (kg)	74.26±6.96	73.51±4.15	72.60±4.49	0.842	0.434
BMI (kg/m ²)	31.87±2.50	31.46±1.23	31.36±1.84	0.696	0.501
Prolactin (ng/ml)	15.87±4.89	13.34±4.18	14.92±4.99	2.582	0.081
E2 (pg/mL)	60.34±4.75	61.20±4.85	61.97±5.74	0.883	0.417
LH (IU/L)	7.83±2.78	7.92±2.13	7.79±2.13	0.026	0.974

Table 2
Clinical presentation of the studied patients in among groups

		Group			P value
		Letrozole (n=35)	Human Menopausal Gonadotropin (n=35)	Letrozole + Human Menopausal Gonadotropin (n=35)	
Weight gain		29 (54.3%)	16 (45.7%)	14 (40.0%)	0.483
Oligomenorrhea		27 (77.1%)	28 (80.0%)	23 (65.7%)	0.351
Hyperandrogenism		17 (48.6%)	17 (48.6%)	14 (40.0%)	0.708
Polycystic ovaries		23 (65.7%)	21 (60.0%)	22 (62.9%)	0.885
PCO on USG	Bilateral	22 (62.9%)	28 (80.0%)	26 (74.3%)	0.263
	Unilateral	13 (37.1%)	7 (20.0%)	9 (25.7%)	

Table 3
Endometrial thickness, E2 or LH after treatment in among groups

	Letrozole (n=35)	Human Menopausal Gonadotropin (n=35)	Letrozole + Human Menopausal Gonadotropin (n=35)	F value	P value
Endometrial thickness (mm)	9.13±0.43	9.38±0.78	10.29±0.87	25.520	<0.001
Noof mature follicles	1.43±0.56	1.74±0.74	2.23±0.77	11.733	<0.001
Prolactin (ng/ml)	69.40±58.43	90.28±68.01	106.23±50.59	3.381	0.038
E2 (pg/mL)	479.91±102.05	441.20±153.57	584.83±132.36	11.255	<0.001
LH (IU/L)	9.73±2.57	10.41±2.81	11.55±1.80	5.001	0.008

Table 4
Effects of different regimens on pregnancy

	Group			P value
	Letrozole (n=35)	Human Menopausal Gonadotropin (n=35)	Letrozole + Human Menopausal Gonadotropin (n=35)	
OHSS cases	2 (5.7%)	4 (11.4%)	4 (11.4%)	0.643
Clinical Pregnancy	11 (31.4%)	12 (34.3%)	19 (54.3%)	0.104
Abortion	2 (5.7%)	3 (8.6%)	2 (5.7%)	0.858
Multiple Pregnancy	2 (5.7%)	2 (5.7%)	4 (11.4%)	0.582