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A STUDY ON OVULATION INDUCTION WITH LETROZOLE IN FEMALES WITH POLYCYSTIC OVARIAN SYNDROME

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Abstract:

Introduction: *Polycystic ovary syndrome (PCOS) is a common endocrine disorder in young women. It manifests itself in a variety of clinical ways and 55%–75% of patients with PCOS are infertile due to chronic anovulation.* ***Aims and objectives:*** *The main objective of the study is to analyze the role of letrozole in female ovulation induction with polycystic ovarian syndrome.* ***Material and methods:*** *This cross sectional study was conducted in Jinnah hospital, Lahore during April 2018 to September 2018 with the permission of ethical committee of hospital. The data was collected from 255 female patients who were suffering from PCOS. Letrozole 2.5 mg/day or CC 50 mg/day was administered from day 3 to day 7 of a spontaneous or progestogen-induced withdrawal of bleeding, plus HMG 75 IU on alternate days daily starting from day 7 and maintained for up to 10 days unless follicle maturity was reached so that human chorionic gonadotropin (hCG) could be administered.* ***Results:*** *The data were collected from 255 female patients. The mean age for this study was 27.28±3.45 years. No statistical difference could be detected for mean age, BMI, or menstrual patterns (amenorrhea or oligomenorrhea) among the three groups of patients. All groups had comparable proportions of primary or secondary infertility, and also the duration of infertility was not significantly different among the three groups. There was also no significant difference with regard to biochemical parameters such as FSH, LH, testosterone plasma levels, LH/FSH ratio, HOMA-IR, and AFC within the three groups. All patients studied had morphological features of PCOS on transvaginal sonographies.* ***Conclusion:*** *It is concluded that letrozole co-treatment with HMG not only reduced the duration of stimulation and total HMG dose needed for stimulation but also achieved a higher incidence of mono follicular growth, demonstrating that this protocol is effective and safe for ovarian induction.*

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INTRODUCTION:

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in young women. It manifests itself in a variety of clinical ways and 55%–75% of patients with PCOS are infertile due to chronic anovulation. Clomiphene citrate (CC) is still the standard drug for inducing or augmenting ovulation [1]. It is not, however, equally successful in all situations. Clomiphene resistance refers to persistence of anovulation after standard CC therapy, which occurs in 15%–20% of patients. Clomiphene citrate may have a negative effect on the cervical mucus and endometrium and is associated with a discrepancy between ovulation and conception rates. Adjuvants to CC such as N-acetyl cysteine (NAC) were used successfully in patients with PCOS, but not in the setting of unexplained infertility [2].

Anovulation is a cause of infertility in up to a quarter of all cases of infertility. Normogonadotropic anovulation classified as World Health Organization (WHO) group II is the most common category of anovulatory infertility [3]. PCOS is the most common in this group and notably the commonest endocrine disorder and cause of anovulation. Insulin resistance is implicated in the ovulatory dysfunction in PCOS by disrupting the hypothalamo-pituitary-ovarian axis [4]. Insulin resistance also leads to other comorbidities such as metabolic syndrome, hypertension, dyslipidemia, glucose intolerance, and diabetes mellitus as well as mental disorders such as depression, anxiety, bipolar disorders and binge eating. Women with PCOS present to the fertility clinic with chronic oligo/anovulation and hyperandrogenism, with attendant negative effects on their fertility [5].

Aims and objectives

The main objective of the study is to analyze the role of letrozole in female ovulation induction with polycystic ovarian syndrome.

MATERIAL AND METHODS:

This cross-sectional study was conducted in Jinnah hospital, Lahore during April 2018 to September 2018 with the permission of ethical committee of hospital. The data was collected from 255 female patients who were suffering from PCOS. The three standard protocols that are usually applied for ovarian induction in CC-resistant infertile women with PCOS in our study center are the use of HMG either alone or in conjunction with letrozole or CC. Letrozole 2.5 mg/day or CC 50 mg/day was administered from day 3 to day 7 of a spontaneous or progestogen-induced withdrawal of bleeding, plus HMG 75 IU on alternate days daily starting from day 7 and maintained for up to 10 days unless follicle maturity was reached so that human chorionic gonadotropin (hCG) could be administered. All patients were monitored by both transvaginal ultrasound measurement of the mean follicular diameter as well as serial assays of estradiol and LH levels on day 11 and every 1–3 days thereafter.

Statistical analysis

Data are presented as mean ± SD. Data analysis was performed by using Statistical Package for Social Sciences (SPSS) for Windows, Version 19.0 (Chicago, IL, USA).

RESULTS:

The data were collected from 255 female patients. The mean age for this study was 27.28±3.45 years. No statistical difference could be detected for mean age, BMI, or menstrual patterns (amenorrhea or oligomenorrhea) among the three groups of patients. All groups had comparable proportions of primary or secondary infertility, and also the duration of infertility was not significantly different among the three groups. There was also no significant difference with regard to biochemical parameters such as FSH, LH, testosterone plasma levels, LH/FSH ratio, HOMA-IR, and AFC within the three groups. All patients studied had morphological features of PCOS on transvaginal sonographies.

Table 1 Patient characteristics in three treated groups

Variable	LE + HMG (n=94)	CC + HMG (n=90)	HMG (n=71)
Age (years)	27.28±3.15	26.79±2.61	26.93±2.75
BMI (kg/m^2)	23.84±2.62	23.70±3.17	24.49±2.85
Amenorrhea, n (%)	27 (29)	28 (31.1)	19 (26.8)
Oligomenorrhea	66 (71)	72 (68.9)	52 (73.2)
Duration of infertility (years)	3.16±1.25	3.21±1.47	3.09±1.45
Primary infertility, n (%)	76 (81.7)	72 (80)	54 (76.1)
LH	8.19±3.37	7.87±3.09	8.03±2.75
FSH	6.37±1.3	6.29±1.32	6.34±1.43
LH/FSH ratio	1.28±0.54	1.26±0.6	1.27±0.51
Testosterone (ng/mL)	0.52±0.17	0.51±0.19	0.54±0.21
HOMA-IR	3.18±1.98	3.26±1.51	3.26±1.83
AFC, n (%)			
12–19 follicles	52 (55.3)	48 (53.3)	29 (40.8)
20–29 follicles	31 (33)	35 (38.9)	38 (53.5)
30–39 follicles	8 (8.5)	6 (6.7)	3 (4.2)
≥40 follicles	3 (3.2)	1 (1.1)	1 (1.4)

DISCUSSION:

Letrozole (4,4′-[1H-1,2,4-triazol-1-ylmethylene]-*bis*-benzonitrile) and anastrozole (2, 2′[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenlene]*bis* (2-methylpropiononitrile)) are third generation aromatase inhibitors [6]. Administering aromatase inhibitors early in the follicular phase can induce ovulation by releasing the hypothalamus or pituitary from estrogen (E) negative feedback on GnRH and gonadotropin secretion, which would stimulate ovarian follicular development [7]. An alternative hypothesis is that aromatase inhibitors may act locally in the ovary to increase follicular sensitivity to FSH by accumulation of intraovarian androgens. In addition, androgen accumulation in the follicle may stimulate insulin-like growth factor I (IGF-I), along with other endocrine and paracrine factors, which may synergize with FSH to promote folliculogenesis [8].

In ovulation induction, the aim should be to achieve the ovulation of a single follicle and hence to reduce the risks of OHSS and multiple pregnancies in women with PCOS. However, the problem of achieving the desired mono follicular ovulation is particularly difficult and acute due to the extreme sensitivity of the polycystic ovary to gonadotrophic stimulation [9]. It was reported that ~10%–20% of cycles were abandoned before completion because of ovarian hyper response, and the ovulation of a single dominant follicle was attained in only ~50% of non-canceled cycles [10].

CONCLUSION:

It is concluded that letrozole co-treatment with HMG not only reduced the duration of stimulation and total HMG dose needed for stimulation but also achieved a higher incidence of mono follicular growth, demonstrating that this protocol is effective and safe for ovarian induction.

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