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Letrozole versus Gonadotropin in Unexplained Infertile Couples Failed to Conceive with Clomiphene Citrate

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Abstract

Background: Unexplained infertility represents about 15% - 20% of infertile couples. Usually, these cases need assistance. Clomiphene citrate is the most used drug for this problem but sometimes pregnancy failed to achieve it, so other options for assistance are gonadotrophin or letrezole. The objective of our study was to compare the pregnancy rate for letrezole and gonadotropin in unexplained infertile women's who failed to conceive with clomiphene citrate. Methods: This prospective quasi-randomized trial was carried out in cytogenetic unite at obstetrics and gynecology department, Zagazig University Hospital. 140 infertile females were included, induction of ovulation by letrozole for half of them and by gonadotrophin for the other half. Results: There was statistically highly significant decrease in duration of stimulation, E2 levels and endometrial thickness at day of HCG in letrezole group, no significant difference between two groups as regard number of follicles and pregnancy rate per cycle, while the cumulative pregnancy rate and the cost of stimulation are significantly higher in gonadotrophin group. Conclusion: In patient with unexplained infertility who failed to conceive with clomiphene citrate, gonadotrophins have a higher pregnancy rate than letrezole. However, pregnancy rate was high enough with lower cost with letrezole to be acceptable and justified its use in this group of patients.

Keywords

Letrozole, Gonadotropin, Infertility, Clomiphene Citrate

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1. Introduction

Infertility is defined as the inability to conceive after one year of a regular unprotected intercourse. The Practice Committee of the American Society for Reproductive Medicine (ASRM) has published guidelines for a standard infertility evaluation. It includes semen analysis, assessment of ovulation, hysterosalpingogram, and if indicated, tests for ovarian reserve and laparoscope. When the results of standard infertility evaluation are normal, practitioners assign a diagnosis of unexplained infertility [1]. For the last couple of decades, clomiphene citrate remained the most popular drug for ovulation induction at the initial stage of management of infertile couples with an ovulation (WHO group II) and unexplained infertility. Though induction of ovulation was achieved in 42% - 80% cases depending on the diagnosis, the conception rate averaged 9% - 13% per cycle through 3 - 6 cycles. The gap between ovulatory and pregnancy rates had variously been attributed to its anti-estrogenic effects on endometrial, cervical mucus, and high LH, resulting in luteal phase dysfunction. Several modifications have been tried to overcome the adverse effects of clomiphene by clomiphene plus therapy. Though the maximum cumulative pregnancy rate was achieved around 31% through 3 - 6 consecutive cycles, the conception rate remained 8% - 14% [2].

Letrozole, an aromatase inhibitor, was introduced into infertility practice in the year 2000 and is regarded as a second line treatment option, particularly in women with clomiphene resistance. Letrozole prevents the conversion of androgens to estrogen, thus releasing the hypothalamic-pituitary axis from the negative feedback of estrogen, resulting in an increase of FSH secretion from the anterior pituitary. The accumulated androgens in the ovary further increase follicular sensitivity to FSH. Importantly, unlike clomiphene citrate, letrozole is devoid of any anti-estrogenic peripheral action. Letrozole is also cleared from the circulation more rapidly. Letrozole at the customary dose of 2.5 mg elicits a mono-follicular response and does not adversely affect either the endometrial or the cervical mucus, due to an absence of a peripheral estrogen receptor blockage. Urinary follicle stimulating hormone (uFSH), recombinant human follicle stimulating hormone (r-hFSH) and human menopausal gonadotrophins (hMG) are two of the gonadotrophin products primarily used for controlled ovarian stimulation (COS) in Assisted Reproduction Techniques (ART), including *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI). Both hMG and r-hFSH have been shown to be effective. r-hFSH is free from urinary protein contaminants, with less immunogenic potential than the urinary-derived medication, and may be preferable from a safety standpoint [3].

Unexplained infertility represents about 15% - 20% of infertile couples. Usually, these cases need assisted reproductive methods. Clomiphene citrate is the most used drug for this problem but sometimes pregnancy failed to achieve it. Other options for assistance are gonadotrophin or letrozole.

2. Aim of the Work

The aim of this prospective quasi-randomized trial is to compare pregnancy rates for letrozole and gonadotropin in unexplained infertile women who failed to conceive with clomiphene citrate.

3. Patients and Methods

This study was performed at Obstetrics and Gynecology department, Zagzag University Hospital, at cytogenic unit. It included 140 females according to the following inclusion criteria.

Inclusion criteria: Patient with age 20 to 35 years; patient with infertility lasting ≥ one year; patent assigned as having unexplained infertility if: patent fallopian tubes detected by hysterosalpigography and/or laparoscopy, normal ovulation confirmed by midluteal progesterone level more than 5 ng/ml, and by normal hormonal profile (F.S.H, L.H, Prolactin and T.S.H) in the three day of menstrual cycle, Male partners have normal semen analysis according to WHO 2010 [4]; Patients considered having clomiphene citrate failure if they did not conceive with at least six cycle of clomiphene citrate [5].

Exclusion criteria: tubal factor infertility; hypothalamic amenorrhea; any hormonal abnormalities serum TSH more than 0.39 and/or less than 4.0 mIU/mL, elevated serum PRL > 26 ng/mL, and basal day F.S.H > 10 m IU/ml; patients with irregular cycles; patients with Ovarian cysts > 20 mm in mean diameter in the second or third day of the menstrual cycle; patients with endometriosis.

4. Methods

All women selected for this study were subjected to: History taking and examination: then, patients were ran-

domized to gonadotropin or letrozole. A quasi-randomization method will be used. Based on the attendance order, patients with odd numbers will be considered group A (letrozole group) and those with even numbers will be considered group B (gonadotropin group); Basal transvaginal ultrasounds examination was performed on cycle day 2 or 3 to exclude cases with ovarian cysts.

The first group included 70 patients were treated with letrozole (Femara, Novartis, East Hanover, NJ), 2.5 mg orally twice per day, from days 3 - 7 of the menstrual cycle, while the second group included 70 patients were treated with day 3 of the menstrual cycle urofollitropin (Fostimon HP; IBSA) 75 IU/ml. I.M will be started with 1 ampoule per day and the dose will be modulated according to the response detected by Transvaginal ultrasounds later on. Transvaginal ultrasounds were performed on day 9 of the menstrual cycle in the letrozole group and on day 7 in the gonadotropin group and were repeated every 2 - 3 day according to follicular growth. Human chorionic gonadotropin (Choriomon; IBSA, Switzerland) (10.000 IU/I.M) was administered when one follicle measured ≥ 18 mm in diameter. HCG injection was concealed if Patients have >3 follicles (15 - 18) mml, E2 > 2500 pg/mL [6]. Sexual intercourse was advised on the day of HCG injection and every other day for 4 days after HCG injection [7]. Pregnancy test was done two day after next missed period. Ultrasound examination was performed 5 weeks after last menstrual period to confirm the presence of fetal cardiac activity and to exclude ectopic pregnancy.

Outcome measures: Primary outcome measure was pregnancy rate per cycle, while secondary outcome included number of follicle in each group, endometrial thickness, miscarriage rate, multiple pregnancies and cost of treatment

Statistical Methods

The collected data organized, tabulated and statistically analyzed using statistical package for social science (SPSS) version 16 (SPSS Inc. USA), running on IBM-Compatible computer using Microsoft Windows® 7 operating system. Quantitative data were represented as mean and standard deviation; sometimes minimum and maximum (range) calculated, while categorical variables were represented as relative frequency. For comparison between groups, independent samples (t) test was used for comparison between quantitative data and Chi square test was used for categorical data. For interpretation of results, p value < 0.05 was considered significant.

5. Results

The present study included 140 females, seeking controlled ovarian stimulation for their primary or secondary infertility. Ovulation induction was the main line of treatment, and cases were divided randomly to one of two groups according to drug used for ovulation induction; the first group was allocated to receive letrozole and the second group received gonadotropin. Results of the present study were represented in the following tables and graphs; letrozole group will be named as group A and gonadotropin group as group B. there was no difference between groups A and B as regard demographic characteristics (**Table 1**). There was statistically extremely significant decrease of duration of stimulation, E2 levels and endometrial thickness at day of HCG stimulation in group A when compared to group B, while there was no significant difference as regard to number of follicles ≥ 18mm (**Table 2**). There was non-significant difference between both groups as regard pregnancy rate at any cycle. As regard to results of pregnancy test after induction, it was positive in 26 cases (18.6%); with significant decrease of positive pregnancy test in group A in comparison to group B (11.4% vs 25.7%) respectively (**Table 3**). There was highly significant increase of cost in group B in comparison to group A, but there was no significant difference as regard to multiple gestation and miscarriage (**Table 4**).

6. Discussion

Although, letrozole has been shown to have good ovulation rate in CC-resistant PCOS women [8], it is poorly studied in ovulation induction in unexplained infertility, especially in clomophine citrate resistant cases. Thus, the present study was designed to compare pregnancy rates for letrozole and gonadotropin in unexplained infertile women's who failed to conceive with clomiphene citrate. It was carried out at Obstetrics and Gynecology department, Zagzag University Hospital, at cytogenic unit. The present study included 140 females, seeking treatment for their primary or secondary infertility. Ovulation induction was the main line of treatment, and after resistance to clomiphene citrate, cases were divided randomly to one of two groups according to drug used for

Table 1. Demographic criteria of both groups.

	Group A	Group B	P value
Age (mean ± SD)	26.78 ± 4.22	27.19 ± 3.97	0.79 (NS)
BMI (mean ± SD)	26.42 ± 0.88	26.38 ± 1.02	0.82 (NS)
Wife's occupation (n, %)			
House wive	63 (90.0%)	62 (88.6%)	0.78 (NS)
Has a job	7 (10.0%)	8 (11.4%)	
Husband age (man ± SD)	32.85 ± 7.08	33.88 ± 6.61	0.37 (NS)
Special habit (smoking; n, %)	25 (35.7%)	28 (40.0%)	0.60 (NS)
Type of infertility			
Primary	65 (92.9%)	62 (88.6%)	
Secondary	5 (7.1%)	8 (11.4%)	0.38 (NS)
Duration of infertility (mean ± SD)	4.35 ± 2.69	5.16 ± 2.64	0.076 (NS)

Table 2. Comparison between studied groups as regard to duration of stimulation, E2 levels, number of follicles and endometrial thickness at the day of HCG stimulation.

	Group A	Group B	t	
Duration of stimulation	8.68 ± 1.12	12.40 ± 1.47	16.73	<0.001* (ES)
E2 levels	717.6 ± 17.4	1028.7 ± 80.85	19.22	<0.001* (ES)
N of follicles ≥ 18 mm	1.75 ± 0.52	1.87 ± 0.67	1.11	0.26 (NS)
Endometrial thickness at day of HCG stimulation	8.97 ± 0.99	10.24 ± 6.58	9.25	<0.001* (ES)

ES = extremely significant.

Table 3. Number of cycles and results of pregnancy rate after each cycle.

	Group A	Group B	X^2	p
Cycle 1	2 (2.9%)	5 (7.1%)	1.35	0.24 (NS)
Cycle 2	2 (2.9%)	3 (4.3%)	0.20	0.64 (NS)
Cycle 3	3 (4.3%)	6 (8.6%)	1.06	0.30 (NS)
Cycle 4 or more	1 (1.4%)	4 (5.7%)	1.86	0.17 (NS)
Cumulative rate	8 (11.4%)	18 (25.7%)	4.72	0.030* (S)

Table 4. Comparison between studied groups as regard to secondary pregnancy outcome

	Group A	Group B	test	P value
Multiple gestation	0 (0.0%)	2 (11.1%)	0.96	0.32 (NS)
Miscarriage	2(25.0%)	7(38.9%)	4.72	0.49 (NS)
Total cost	190 ± 0.00	225.50 ± 80.24	5.86	<0.001* (ES)

ovulation induction; the first group was allocated to receive letrozole and the second group received gonadotropin.

Concerning demographic criteria, there was no significant differences between both groups. The mean E2 levels at the day of HCG supplementation was 717.6 ± 17.4 in group A compared to 1028.7 ± 80.85 in group B, with extremely significant increase in group B. These results are comparable to those reported by [9] who re-

ported that, cases with letrozole induction had significantly (P = 0.0001) decreased levels of terminal E2.

In the present study, there was non-significant difference between group A and B as regard to number of follicles ≥ 18 mm in diameter in diameter (1.75 ± 0.52 vs 1.87 ± 0.67 respectively), and these results are in agreement with one randomized trial using letrozole 5mg daily for 5 days compared to 150 IU daily of gonadotropins, beginning at day 3 of the cycle, with later adjustment based on monitoring results, and there was no difference in mature follicle number (1.3 versus 1.8) [10]. Also, Haq Nawaz *et al.* [11] reported that, the median number of follicles > 18 mm in diameter on the day of HCG administration were comparable among the two groups.

In the present work, there was significant decrease of endometrial thickness in group A when compared to group B (8.97 ± 0.99 vs 10.24 ± 0.58 respectively). Quintero *et al.* [12] reported that endometrial thickness was greater in the gonadotropin group when compared to the letrozole groups (8.6 ± 0.3 vs. 7.5 ± 0.2 mm, P = 0.001). In study by Gregoriou *et al.* [10] the endometrial stripe in the recombinant FSH group was significantly thicker than in the letrozole group (8.6 vs. 7.1, P < 0.01). This was expected and it could be attributed to the significantly higher levels of E2 recorded in the gonadotropin group. Our results are also in agreement with the study by Healey *et al.* [13].

In the present work, there was non-significant difference between both groups as regard pregnancy rate at any cycle. Results of the present study are in contradiction to that of Baysoy *et al.* [14] who reported that, pregnancy rates were not significantly different between the two groups. There were pregnancies in seven of the 38 letrozole-IUI cycles (18.42%) and in six of the 38 HMG-IUI cycles (15.78%). In addition, Speroff and Fritz [15] reported that, pregnancy rates of 11.4% per cycle are often considered acceptable for infertility treatments. Our findings suggest that letrozole is a possible second-line treatment after failure to conceive with CC. In contradiction to results of the present study, and when looking at women with unexplained infertility utilizing letrozole versus gonadotropins, the randomized controlled trials are again consistent, showing similar pregnancy rates but with significantly reduced costs in the letrozole group. In one randomized trial, letrozole 5 mg daily for 5 days was compared to 150 IU daily of gonadotropins, beginning at day 3 of the cycle, with later adjustment based on monitoring results. Pregnancy rates were not significantly different (8.9% for letrozole, 14% for gonadotropins) [10].

As regard to multiple gestations, in only reported in 2 cases out of 18 get pregnant cases (11.1%) in group B, group A had none with multiple gestation and there was no significant difference between groups. These results can be explained by the hypoestrogenic state created by letrozole should not last late into the follicular phase of the menstrual cycle due to its short half-life, creating a higher likelihood of *monofollicular* growth [16]. Miscarriage rate in the present study appears to be high at (34.6%) with insignificant decrease in group A in comparison to group B (25.0% vs 38.9% respectively). However, early pregnancy detection was performed with serum quantitative pregnancy hormone levels 14 days after ovulation triggering. Studies evaluating early miscarriage rates have documented the frequency of pregnancy wastage to be between 30% and 66% [15]. Therefore, the miscarriage rate in this study may not differ from baseline levels.

In the present study, there was statistically highly significant decrease of cost (mean 190 EP) in leterozole group in comparison to other group induced with gonadotropin (mean 225 EP). These results are in accordance with Mukherjee *et al.* [9] who reported significant low cost of induction by leterozole in comparison to gonadotropins regardless of success rate.

7. Conclusion

In short, results of the present study revealed that, in patients who failed to conceive with CC, gonadotropins have a higher PR for ovulation induction than letrozole. However, PR was high enough with letrozole to be acceptable and justified its use in this population of patients.

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