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A COMPARATIVE RESEARCH TO ASSESS THE EFFECTIVENESS OF LETROZOLE AND CLOMIPHENE CITRATE AMONG INFERTILE ANOVULATORY WOMEN

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Abstract:

Objective: The purpose of the research was to compare clomiphene citrate versus letrozole for acquiring auspicious gravidity in anovulatory infertile females.

Material and Methods: The mode of the research was comparative which was carried out at Jinnah Hospital, Lahore from April 2017 to January 2018. Total numbers of anovulatory infertility patients in our research are two-hundred and twenty-four having age eighteen to forty years. Entire those patients having a former record of operation, hyperprolactinemia and hypothyroidism were not included in the research. Researcher divides the enrolled patients for research into two categories, category "A" (clomiphene citrate) and category "B" (letrozole) by applying the lottery procedure. A resultants variable such as affectivity was recorded.

Results: The average age of the females in clomiphene citrate group was (26.72 ± 6.02) years and in letrozole group was (26.87 ± 6.33) years. One hundred and forty-eight (66.07%) were between eighteen to thirty years of age. The average interval of infertility was (3.47 ± 2.21) years. The average interval of infertility in clomiphene citrate group was (3.23 ± 2.19) years and in letrozole group was (3.68 ± 2.34) years. The effectuality of clomiphene group (Group "A") was nineteen (16.96 %) whereas in letrozole group (Group "B") was thirty-seven (33.04%) with P value =0.005.

Conclusion: The research determined that letrozole is ameliorated and more productive in term of accomplishing gestation in the treatment of anovulatory infertility.

Keyword: Hypothalamic-Pituitary-Ovarian (HPO), Anovulatory, Selective Estrogen-Receptor Modulator (SERM), Non-Polycystic Ovarian Syndrome (PCOS).

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INTRODUCTION:

Ovulation is the outcome of a development procedure which takes place in the HPO axis and is organized by a neuroendocrine cascade finalized in the ovaries [2]. Ovulation abnormality is a major factor of genial collapse in infertile couples. The expansion of this malady in infertile females is about thirty to forty percent. Any state weather primary as well as secondary, the consequences in either a constant rise or deficient achievements of estrogen level could restrain ovulation via interruption of the system that's generate LH surge. To obtain the correspondent variations into the cycle, the inclination and declination of estradiol level are compulsory. The hypothalamic-pituitary-ovarian axis is the aim of the first line ovulation induction treatment, which contains oral prolificacy drugs i.e. letrozole and clomiphene citrate are two most general, could be enhanced by HCG [3, 7, 5, 10]. Injectable prolificacy drugs i.e. Follistim, Repronex, Gonal-f could be utilized with intrauterine insemination or in-vitro procreation [6, 7, 9]. However, oral prolificacy medicines are the most general habituated treatment for ovarian abnormality throughout the world.

Clomiphene citrate is SERM that disaffect the negative response of estrogen at the hypothalamus with a subsequent rise in ovarian stimulation via endogenous gonadotropin [8]. Clomiphene has some limitation, which contains its entire poor effectiveness, comparatively increased gestation rate and an unwanted drawbacks profile containing hot flushes and mood variation [5, 8]. Letrozole is counted as a non-steroidal aromatase inhibitor, which obstructs estrogen synthesis through the transformation of androgens via the action of aromatase enzyme thus, instantly influence HPO operation and accelerate gestation rate by ovarian stimulation. Probable benefits of aromatase inhibitor over selective estrogen receptor modulator contains an additional endometrium, psychological hormonal stimulation, better limitation profile with infrequent vasomotor as well as mood indicator, lesser multiple gestation rate and fast clearance [8,10]. Several types of research have presented an expressive variation between gestation, ovulation rate and huge miscarriage rate in those patients who are undergoing clomiphene treatment. Few prospective researches have been conducted and finding displayed that as compare to clomiphene, letrozole cycle has substantially huge gestation rate [2, 3]. The research conducted by Ibrahim MI presented gestation rate of (23.07%) & (10.68%) in letrozole and clomiphene group respectively. It is verified from the literature that letrozole had an absolute role in those anovulatory females who have not replied to clomiphene treatment [4, 5, 8, 9]. But its task as a clomiphene substitute as initial step treatment continues to be argued [7, 10]. So that there were requirements of additional research to diagnose the best therapy for ovulation induction as well as obtaining a prosperous gestation which might be suggested to the patients in the near future. So, the purpose of the research was to compare clomiphene citrate versus letrozole for acquiring auspicious gravidity in anovulatory infertile females. Therefore a few practical approvals could be formulated to attain multiple of gestation in anovulatory infertile females with most efficient treatment command. Those patients having birth control free sexual intercourse for greater than one year and still not achieved gravidity even of having usual pelvic ultrasonography, on hysterosalpingography bilateral standard tubal effectiveness as well as a better male factor, then it is called anovulatory infertility. Effectiveness was calculated in term of the appearance of gestation by calculating the β-HCG level of ≥ 5mlU/ml at 5th day after a missed menstrual interval or else assumed as "NO".

MATERIAL AND METHODS:

The mode of the research was comparative which was carried out at Jinnah Hospital, Lahore from April 2017 to January 2018. Total numbers of anovulatory infertility patients in our research are two-hundred and twenty-four having age eighteen to forty years. Entire those patients having a former record of operation, hyperprolactinemia and hypothyroidism were not included in the research. Written approval was taken from the review panel and all those patients who are being checked in OPD of the hospital and fulfilling the prerequisite of the research was enrolled as well as informed consent were also attain from entire participants. After that enrolled patients were given choice to take one slip from entire mixed up slips (1/2 slips contain alphabet "A" and ½ "B") and was adjusted in that particular group, which they opted (A or B). the patients in category "A" was advised to take clomiphene citrate orally once in a day up to five days (three to seven) of menstrual cycle and continue till five menstrual cycle as well as the patients in category "B" was advise to take 2.5mg letrozole once a day on days three to seven of menstrual cycle up till five menstrual cycle. Entire patients of both the categories were examined after finishing of every rotation to identify the happening of gestation, which was verified by gauging the β-HCG level at 5th day after the first missed menstrual duration and effectuality of every group was recorded as pre operational definition. All the facts and figure were noted on predesigned Performa. The composed facts were evaluated by

SPSS. Average and SD was measured for quantitative variables i.e. interval of infertility. Periodicity and the percentage was measured for qualitative variables i.e. effectuality (yes/no). to find out effectiveness in both categories chi-square test was used. Result changer such as an interval of infertility and age, fatness were controlled via stratification as well as post stratification. Chi square test was used to find out the consequences of these on effectuality. P value ≤0.05 was assumed as substantial.

RESULTS:

The age range in our research was from eighteen to forty years with (26.76 ± 6.19) years of average age. The average age of the females in clomiphene citrate group was (26.72 ± 6.02) years and in letrozole group was (26.87 ± 6.33) years. One hundred and forty-eight (66.07%) were between eighteen to thirty years of age. The average interval of infertility was (3.47 ± 2.21) years. The average interval of infertility in clomiphene citrate group was (3.23 ± 2.19) years and in letrozole group was (3.68 ± 2.34) years. Maximum no of the patient's one-hundred and forty (62.50%) had less than five years of infertility interval. The effectuality of clomiphene group (Group "A") was nineteen (16.96 %) whereas in letrozole group (Group "B") was thirty-seven (33.04%) with P value =0.005.

Table – I: Age and Infertility Duration

Age and Infertility Duration		**Group - A (112)**		**Group - B (112)**		**Total (224)**	
		No	**%**	**No**	**%**	**No**	**%**
Age	18 - 30 Years	73	65.18	75	66.96	148	66.07
	31 - 40 Years	39	34.82	37	33.04	76	35.97
Duration of Infertility	< 5 Years	71	63.39	69	61.61	140	62.5
	> 5 Years	41	36.61	43	38.39	84	37.5
Average Values		**Mean**	**±SD**	**Mean**	**±SD**	**Mean**	**±SD**
Age (Mean ± SD)		26.72	6.02	26.87	6.33	26.76	6.19
Duration of Infertility (Mean ± SD)		3.23	2.19	3.68	2.34	3.47	2.21

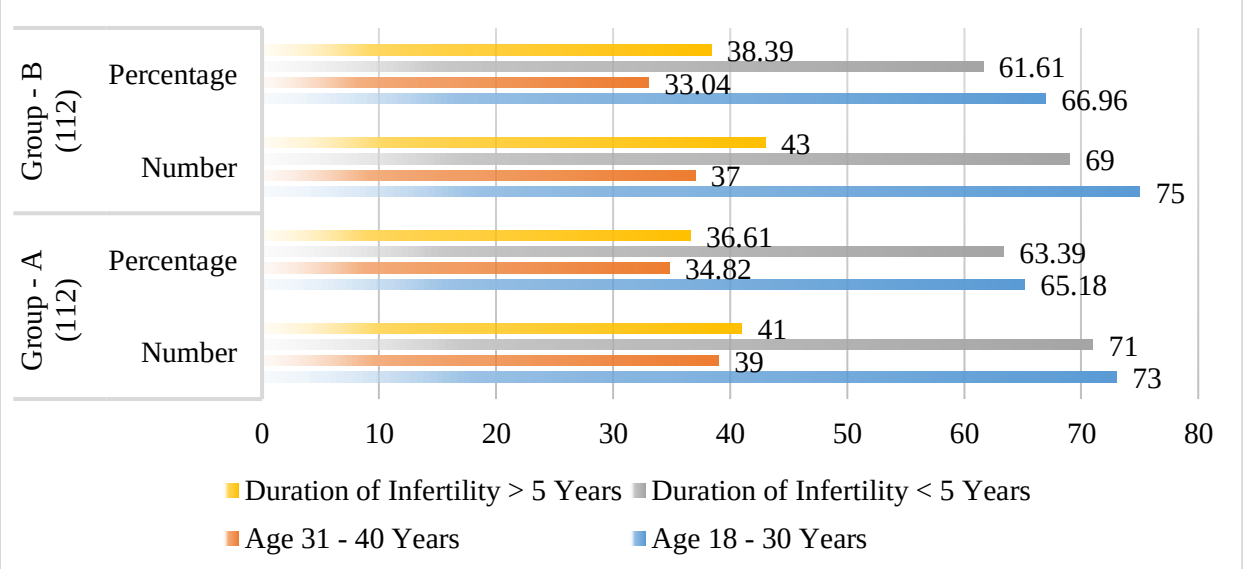


Table – II: Group-Wise Obesity Comparison

Obesity	Group - A (112)		Group - B (112)	
	Number	Percentage	Number	Percentage
Yes	65	58.04	67	59.82
No	47	41.96	45	40.18

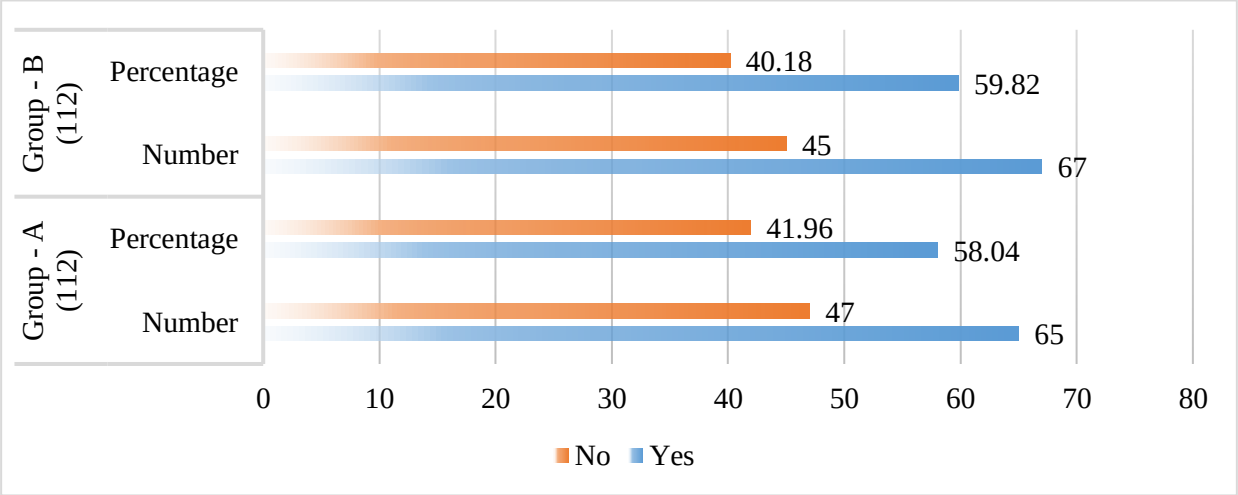


Table – III: Group-Wise Efficacy Comparison

Efficacy	Group - A (112)		Group - B (112)	
	Number	Percentage	Number	Percentage
Yes	19	16.96	37	33.04
No	93	83.04	75	66.96

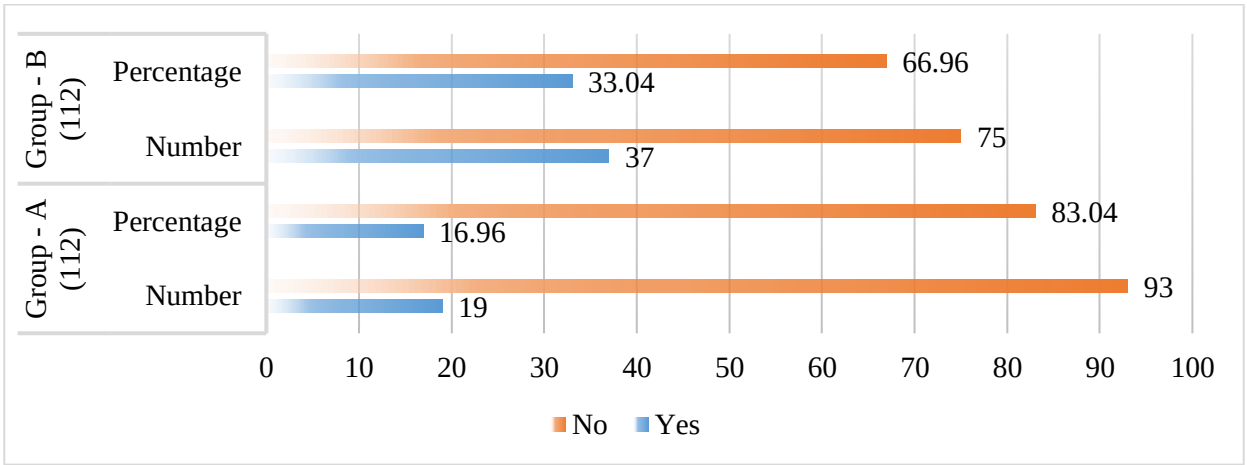
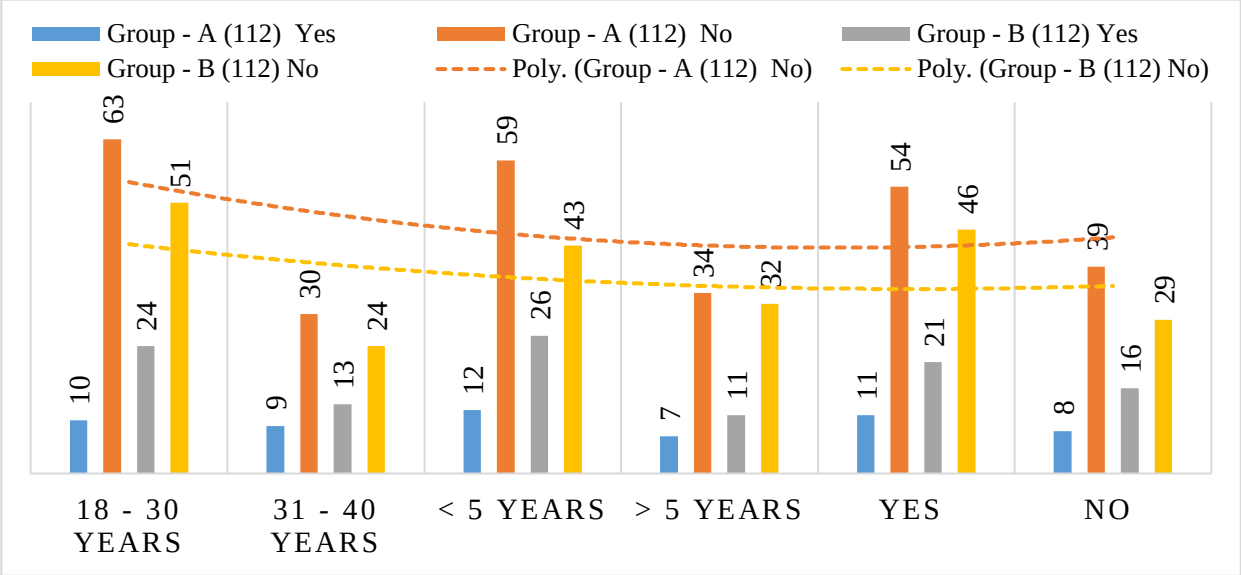


Table – IV: Age, Infertility Duration and Obesity

Efficacy		Group - A (112)		Group - B (112)		P-Value
		Yes	No	Yes	No	
Age	18 - 30 Years	10	63	24	51	0.008
	31 - 40 Years	9	30	13	24	0.247
Infertility Duration	< 5 Years	12	59	26	43	0.006
	> 5 Years	7	34	11	32	0.342
Obesity	Yes	11	54	21	46	0.053
	No	8	39	16	29	0.043



DISCUSSION:

Anovulatory is the most general factor of infertility in females. Numbers of medicines are utilized for induction ovulation between anovulation PCOS. SERM is the first line of traditional therapy [11]. In 1956 the clomiphene citrate has been establishing [12]. Clomiphene citrate is the first ovulation induction technique in females with anovulatory infertility. It has been the selected medication for oral ovulation induction around the conclusive fifty years since 1926. [13]. In eighty percent of anovulatory females, ovulation could be induced by clomiphene citrate, however, just forty percent of females become gravid [14]. Gestation rate per cycle can be ten to twenty percent and reached up to sixty percent after six cycles and nine-seven percent after ten cycles [15]. Unluckily twenty to twenty-five percent of the females are renitent to clomiphene citrate so consequences are ovulation failure [16]. FSH level is augmented by letrozole so consequently mature follicles multiple numbers also augmented and it has not any opposite endometrial consequences because they halved life is smaller than clomiphene citrate resultantly augmented gestation rate [17]. In a number of researches, letrozole was utilized in PCOS with the objective of ovulation induction. However, facts in a non-polycystic-ovarian-disease patient are insufficient. The purpose of the research was to compare clomiphene citrate versus letrozole for acquiring auspicious gravidity in anovulatory infertile females. Age range in our research was from eighteen to forty years with 26.76±6.19 years of average age. The average age of the females in the clomiphene citrate group was 26.72±6.02 years and in letrozole group was 26.87±6.33. One hundred and forty-eight (66.07%) were between eighteen to thirty years of age. Effectuality of clomiphene group (Group "A") was nineteen (16.96 %) whereas in letrozole group (Group "B") was thirty-seven (33.04%) with P value =0.005. The research conducted by Ibrahim MI presented gestation rate of (23.07%) & (10.68%) in letrozole and clomiphene group respectively. In a research

conducted on one-hundred & fifty anovulatory infertile females who had detached PCOS shuffle to three categories. Clomiphene citrate (50mg to150mg) was taken by group "A" for five days, tamoxifen (10mg to 30mg) was used by group "B" for five days similarly letrozole (2.5mg to 7.5mg) was used by group "C" for five consecutive days up till ovulation was induced. Medicines are continuously used for seven days if ovulation unsuccessful to happen within five days of therapy. Sixty (73.4%) was entire ovulation rate, this ovulation rate in group "A" was thirty-nine (78%), twenty-four (68%) in group "B" and thirty-seven (74.0%) in group "C". Gestation rate in group "A" was thirty-two (64%), twenty (40.0%) in group "B" and thirty-five (50.0%) in group "C". Moreover thirty-two (44%) was live birth rate in group "A", seventeen (34%) in group "B" and thirty-one (42.0%) in group "C". with clomiphene citrate the miscarriage rate was ten (20%) whereas in tamoxifen group it was three (6%) and in letrozole group it was four (8%) with P value =0.05 [18]. One additional research conducted by Mitwally and Casper analyzed letrozole usage with exogenic FSH in twelve patients with unidentified infertility and record of poor ovarian reaction to FSH in at least two earlier cycles [19]. Former poor respondent were those who had< three follicles greater than or equal to 18mm on HCG control day [20]. 5mg/day of letrozole day was administrated from 2nd to 6th day and gonadotropin therapy 75 iU/day was commenced on 7th to the 9th day. Researcher conducted intrauterine insemination in each cycle. Batter feedback was recorded to exogenic gonadotropin stimulant with the therapy of letrozole by inferior gonadotrophic dosage and it was connected with increased number of mature follicles. Three (21%) gestation was obtained. in another research conducted by Healy et al recorded uniform results in two-hundred and five IUI cycles. Augmentation to letrozole to FSH therapy reduced FSH demands as well as raise preovulatory follicles number [21]. Atay V et al mixed one-hundred and six females with polycystic-ovarian-disease (55/51) to take weather 2.5mg letrozole or 100mg/day clomiphene citrate [22]. The ovulation rate (82.4%) versus (9.1%) with P =0.03 as well as clinical gestation rate (21.6%) versus (9.1%) with P value =0.03 were substantially over in letrozole category versus clomiphene citrate. Moreover, authors approved letrozole as an appropriate first-line procedure. In one additional RCT (Randomized control trial) letrozole versus clomiphene citrate was compared by Bayer V et al as an inducing element of the first line [23]. There were no important dissimilarities in either the clinical gestation rate or ovulation rate in both the categories (65.7%) Vs (74.7%) and (9.1%) Vs (7.4%). Begum et al enrolled those females for his randomized control trail who does not given a response to clomiphene 100mg [24]. The study group was given letrozole of 7.5mg whereas clomiphene citrate 150mg was given to control group]. Not surprisingly, the ovulation rate in the study group (62.5%) were substantially higher with reference to clomiphene arm (37.5%). In one more research by Hussain et al, gestation rate identified in the letrozole category (25.3%) was too greater with respect to clomiphene citrate category (16.0%) [25]. Additionally, that was not statistically expressive. In a local RCT, the average age of females in clomiphene category was 26.67±4.23 as well as in letrozole category it was 26.24±4.18. the average marriage period in letrozole and clomiphene category was 4.26±2.12 and 4.06±1.95 years respectively along with (21.70%) and (10.38%) efficacy.

CONCLUSION:

The research determined that letrozole is ameliorated and more productive in term of accomplishing gestation in the treatment of anovulatory infertility. So, we suggested that as a first line treatment, letrozole must be utilized in anovulatory infertile females for the purpose of attaining multiple pregnancies.

REFERENCES:

1. Fisher SA, Reid RL, Van Vugt DA, Casper RF. A randomized double-blind comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on ovulatory function in normal women. Fertil Steril. 2002;78(2):280–5.
2. Healey S, Tan SL, Tulandi T, Biljan MM. Effects of letrozole on superovulation with gonadotropins in women undergoing intrauterine insemination. Fertil Steril. 2003;80(6):1325–9.
3. Atay V, Cam C, Muhcu M, Cam M, Karateke A: Comparision of Letrozole and Clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. J Int Med Res. 2006, 34: 73-76.
4. Bayar U, Basavan M, Coskun A, Gezer S: Use of aromatase inhibitors in Patient with polycystic ovary syndrome: a prospective randomized trial. Fertil Steril. 2006, 86: 1447- 1451.
5. Begum Rashida M, Ferdous J, Begum A, Qadir E: Comparison of efficacy or aromatase inhibitor and clomiphene citrate in polycystic syndrome. Fertil Steril. 2009, 92: 853-857.
6. Hussain NHN, Ismail M, Zain MM, Yeu PC, Ramli R, Mohammad WMZW.A randomized controlled trial of Letrozole versus Clomiphene citrate for induction of ovulation in polycystic ovarian syndrome (PCOS): a Malaysian experience. Open J Obstet Gynecol 2013; 3:11-7.
7. Akbari S, Ayazi RM, Ayazi RF. Comparing of letrozole versus clomiphene citrate combined

with gonadotropins in intrauterine insemination cycles. Iran J Reprod Med. 2012; 10:29-32.
8. Sakhavar N, Kaveh M, Sadeghi K. The impact of letrozole versus clomiphene citrate on uterine blood flow in patients with unexplained infertility. J Family Reprod Health. 2014; 8:1-5.
9. Kar S. Clomiphene citrate or letrozole as first-line ovulation induction drug in infertile PCOS women: a prospective randomized trial. J Hum Reprod Sci. 2012; 5:262-5.
10. Banerjee Ray P, Ray A, Chakraborti PS. Comparison of efficacy of letrozole and clomiphene citrate in ovulation induction in Indian women with the polycystic ovarian syndrome. Arch Gynecol Obstet. 2012; 285:873-7.
11. Kamath MS, George K. Letrozole or clomiphene citrate as the first line for anovulatory infertility: a debate. ReprodBiolEndocrinol. 2011; 9:86.
12. Brown J, Farquhar C, Beck J, Boothroyd C, Proctor M, Hughes E. Oral anti-estrogen and medical adjuncts for subfertility associated with anovulation. Cochrane Database Syst Rev. 2009;1 CD002249. [PubMed]
13. Fisher SA, Reid RL, Van Vugt DA, Casper RF. A randomized double-blind comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on ovulatory function in normal women. Fertil Steril. 2002; 78:280–285.
14. Sipe CS, Davis WD, Maifeld M, Van Voorhis BJ. A prospective randomized trial comparing anastrozole and clomiphene citrate in an ovulation induction protocol using gonadotropins. Fertil Steril. 2006; 86:1676– 1681.
15. Richard JP, Steiner AZ, Terplan M. Comparison of tamoxifen and clomiphene citrate for ovulation induction: a meta-analysis. Hum Reprod. 2005; 20:1511–1515.
16. Messinis IE. Ovulation induction: a mini review. Hum Reprod. 2005; 20:2688–2697.
17. Quintero RB, Urban R, Lathi RB, Westphal LM, Dahan MH. A comparison of letrozole to gonadotropins for ovulation induction, in subjects who failed to conceive with clomiphene citrate. Fertil Steril. 2007; 88:879– 885.
18. Al-Fadhli R, Sylvestre C, Buckett W, Tan SL, Tulandi T. A randomized trial of superovulation with two different doses of letrozole. Fertil Steril. 2006; 85:161–164.
19. Seyedoshohadaei F, Zandvakily F, Shahidi S. Comparison of the effectiveness of clomiphene citrate, tamoxifen and letrozole in ovulation induction in infertility due to isolated anovulation. Iran J Reprod Med. 2012 Nov; 10(6): 531–536.
20. Mitwally MF, Casper RF. Aromatase inhibition improves ovarian response to follicle-stimulating hormone in poor responders. Fertil Steril. 2002;77(4):776–80.
21. Ibrahim MI, Moustafa RA, Abdel-Azeem AA. Letrozole versus clomiphene citrate for superovulation in Egyptian women with unexplained infertility: a randomized controlled trial. Arch Gynecol Obstet. 2012; 286:1581-7.
22. El-Gharib MN, Mahfouz AE, Farahat MA. Comparison of letrozole versus tamoxifen effects in clomiphene citrate-resistant women with the polycystic ovarian syndrome. J Reprod Infertil. 2015; 16:30-5.
23. Badawy A, Abdel Aal I, Abulatta M. Clomiphene citrate or letrozole for ovulation induction in women with polycystic ovarian syndrome: a prospective randomized trial. Fertil Steril. 2009; 92:849-52.
24. Roy KK, Baruah J, Singla S, Sharma JB, Singh N, Jain SK, et al. A prospective randomized trial comparing the efficacy of Letrozole and Clomiphene citrate in induction of ovulation in polycystic ovarian syndrome. J Hum Reprod Sci. 2012; 5:20-5.
25. Eftekhar M, Mohammadian F, Davar R, Pourmasumi S. Comparison of pregnancy outcome after letrozole versus clomiphene treatment for mild ovarian stimulation protocol in poor responders. Iran J Reprod Med. 2014; 12:725-30.