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Impact of clomiphene citrate, tamoxifen and letrozole to induce ovulation in anovulatory women with polycystic ovary syndrome on endometrial thickness and clinical pregnancy rates, a two center cohort study

Abstract

Purpose: to compare between clomiphene citrate, tamoxifen and letrozole as a first line drug to induce ovulation in anovulatory women with polycystic ovary syndrome

Methods: 185 infertile women already diagnosed as anovulatory infertility by ultrasound and serum progesterone on day 21recruited from outpatient infertility clinic of Menoufia University Hospital, Egypt and King Abdel-Aziz Airbase Hospital, KSA divided into 3 groups: Group 1, 62 patients who received clomiphene citrate 100 mg daily for 5 days starting for day 2 to day 6 of cycle. Group 2, 61 patients who received tamoxifen 40 mg daily for 5 days starting from day 2 to day 6 of the cycle. Group 3, 62 patients who received letrozole 5 mg of the drug daily for 5 days, starting from day 2 to day 6 of the cycle.

Results: no significant difference between the 3 groups regarding age, duration of infertility and the presence of obesity. Mean endometrial thickness: group1: 7.52mm, group2: 9.38mm, group 3: 9.44mm ($p<0.001$). Mean number of follicles: group1: 1.54, group2: 1.22mm, group 3: 1.08 ($p<0.05$). Pregnancy rate for group 1, 2 and 3: 16 (25.8%), 21 (34.4%) and 25 (40.3%) respectively ($p>0.05$). mean midluteal serum progesterone: group1: 22.69ng/dl, group2: 29.16ng/dl, group 3: 28.08ng/dl ($p= 0.001$).

Conclusion: Tamoxifen should be the first choice to induce ovulation in anovulatory PCO women.

Keywords: infertility, anovulation, polycystic ovary, induction of ovulation, clomiphene citrate, tamoxifen, letrozole

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Introduction

Up to 15 % of couples have the inability to conceive despite regular sexual intercourse.[1] Ovulatory disorders; either anovulation or oligo-ovulation constitutes a major cause for infertility.[2] Polycystic ovary syndrome PCO, the commonest endocrinologic abnormality during childbearing period, constitutes the major cause of anovulation related infertility contributing up to 95 % of ovarian factors of infertility.[3] The problem in PCO women is not the count of primordial follicles; the main problem is in the development and maturation. Maturation is arrested revealing multiple follicles of almost homogenous diameter between 4 and 8 mm without development of dominant follicle, hence, anovulation and infertility.[4] Induction of ovulation is the principal treatment for those women, clomiphene citrate, a selective estrogen receptor modulator, has been used as a first choice drug for long time, it acts centrally, on the hypothalamus, antagonistic effect on estrogen receptors, so releasing the hypothalamus from negative feedback, hence increasing gonadotrophin release.[5] Tamoxifen is another selective estrogen receptor modulator used for that purpose with nearly similar outcomes and with less side effect profile.[6] Since 2001letrozole has been introduced to be used for ovulation induction, a drug which blocks conversion of androgen to estrogen.[7] The aim to get pregnant requires ovulation, fertilization and well receptive endometrium. More than one study support the correlation between endometrial thickness at midcycle and in pregnancy rates and outcomes in ART cycles.[8–10] So endometrial thickness in midcycle is an important indicator for successful implantation and pregnancy outcomes, also we noticed in our practice that mid luteal serum progesterone is higher in women induced with tamoxifen.

The aim of the study was to compare between the effect of clomiphene citrate, tamoxifen and letrozole on endometrial thickness and clinical pregnancy rate when used to induce ovulation in anovulatory women with PCO.

Patients and methods

This prospective cohort study was conducted at Menoufia university Hospital, Menoufia, Egypt and KAAB military Hospital, Saudi Arabia between December 2014 and April 2017on 185 women, recruited from the Outpatient Infertility Clinic. Sample size was calculated based on the incidence of PCO in anovulatory infertile women from the literature,[11] 80% of anovulatory infertility, so about 32% of all infertile women referred to our tertiary hospital per year at 99% confidence level , 5% CI, 170 patients were required. For drop out cases 200 women were included and 185 women completed follow up. This study followed the Ethical Committee rules of Obstetrics

and Gynecology in Menoufia University Hospital and approved by the study ethical committee Menoufia faculty of medicine and KAAB Hospital. All the procedures, in this study were conducted in compliance with the ethical principles for medical research involving human subjects of the World Medical Association (Declaration of Helsinki). Infertile women with polycystic ovary syndrome PCO who were already diagnosed to be anovulatory by ultrasound and progesterone on cycle day 21 and met the inclusion criteria: Age from 18 to 35 years, Patients with anovulatory PCO chosen according to Rotterdam consensus.[12] Normal uterus and patent fallopian tubes proved by Hysterosalpingography (HSG), Normal semen analysis of the husband, Normal serum prolactin and thyroid stimulating hormone TSH were eligible to participate in the study. Women with hyperprolactinemia, thyroid dysfunction, active liver diseases, renal disease, Documented pelvic diseases as endometriosis, any ovarian pathology, hydro- or pyo-salpinx and uterine fibroids, previous history of ovarian drilling and those who refused to participate were excluded from the study. Explanation of the study procedures was done to all participants and informed consent was obtained from each woman. The participants were randomly allocated by the study statistician (using the online research randomizer software http://www.graphpad.com/quickcalcs/index.cfm) into 3 groups:

a. **Group 1: 62 patients** This group included 100 patients who are under ovulation induction with clomiphene citrate. Patients took 100mg of drug daily for 5 days starting for day 2 to day 6 of cycle. Each tablet of the drug is 50mg. So, patients took the dose in form of 2 tablets together after breakfast for three cycles.

b. **Group 2: 61 patients** This group included 100 patients who are under ovulation induction with tamoxifen. Patients took 40mg of the drug daily for 5 days starting from day 2 to day 6 of the cycle. Each tablet of the drug is 20mg. So the patients took the dose in the form of 2 tablets together after breakfast for three cycles.

c. **Group 3: 62 patients** This group included 100 patients who are under ovulation induction with letrozole. Patients took 5mg of the drug daily for 5 days, starting from day 2 to day 6 of the cycle; each tablet of the drug is 2.5mg. So the patients took the dose in the form of 2 tablets together after breakfast for three cycles.

For All selected women, the following was done: Detailed history, Physical examination including general, abdominal and local examination, baseline pelvic Ultrasound, baseline serum FSH, LH, E2, free testosterone, estradiol, TSH, free T3 and T4 and prolactin, HSG, Semen analysis to rule out male factor, husband's semen analysis was considered normal according to WHO 2010 criteria.[13] Vaginal ultrasound folliculometry at 9th day of menstrual cycle, then follow up every other day until the mean diameter of the largest follicle reaches 18mm, Triggering ovulation was made by intramuscular injection of 10,000IU human chorionic gonadotropin (HCG; Profasi HP®, Serono S. A., Geneva, Switzerland) when the leading follicle reached ≥18mm diameter. Free sexual intercourse was encouraged from the day of HCG administration only in cases when no more than three follicles bigger than 17mm were observed; then, HCG injection was not administered and protected sexual intercourse was recommended in order to avoid high order multiple conception. The mean number of follicles over the 3 cycles was calculated then the endometrial thickness in mm was measured in the sagittal view as the maximum thickness between the highly reflective interface of the endometrial-myometrial junction and the mean endometrial thickness over the 3 cycles was taken. If no dominant follicle detected till day 15 of the cycle, transvaginal ultrasound was continued every other day till day 20 and the endometrial thickness was measured, if still no dominant follicle till that time, patient was considered as failed induction. On cycle day 22 serum progesterone was measured. Regarding the number of mature follicles, endometrial thickness and serum progesterone in the mid luteal phase, the mean over the 3 cycles was taken and if pregnancy occurred after one cycle, only single reading was taken and if pregnancy occurred after two cycles, the mean value for the two cycles was calculated.

Outcome measures: Primary outcome measures were the endometrial thickness, Number of mature follicles in each group and mid luteal serum progesterone and Clinical pregnancy rate, Secondary outcome measure; failed induction, cycle cancelation, ovarian hyper stimulation syndrome. Data were collected in a special form for each patient.

Statistical analysis: Results were statistically analyzed by SPSS version 20(SPSS Inc., Chikago, IL, USA).The Shapiro Wilk test was performed to test the Gaussian distribution of continuous variables. Normally distributed numerical data were presented as mean and standard deviation. Non-normally distributed data were presented as median and range. Qualitative data were presented as the number and percentage. F test was used for parametric data. Kruskal-Wallis was used for non-parametric data. Post hoc test was used after F test and Kruskal-Wallis test to detect the least significant difference between the studied groups. Chi-Squared (χ^2) was used for qualitative variables. P value <0.05 is considered significant.

Results

i. Table 1 shows no significant difference between the three groups regarding age, duration of infertility and the presence of obesity.

ii. Table 2 shows no significant difference between the three groups regarding basic endometrial thickness, regarding preovulatory endometrial thickness group (2) and group(3) have significantly greater endometrial thickness than group (1), on the other hand, group (1) has significantly greater mean number of follicles and for all parameters, no significant difference between group (2) and group(3).

iii. Table 3 shows that the highest pregnancy rate is in group (3) then group (2) and the least is in group (1) but this difference is not significant. Regarding mid luteal progesterone level, group (2) and group (3) have significantly higher level than group (1).

Table 1 Comparison between the studied groups regarding their characteristics

	Groups						Test of sig	P value
	CC[1] (No.=62)		Tamox[2] (No.=61)		Letrozol[3] (No.=62)			
	Mean±SD		Mean±SD		Mean±SD			
Age (years)	26.91 ±2.69		27.24 ±2.75		27.50 ±2.99		F=0.65	0.519
Duration of infertility (years)	3.82±1.44		4.06 ±1.35		3.96 ±1.42		Kruskal-Wallis=1.01	0.602
Obesity (No & %)	12	14.9	8	13.1	10	16.1	χ^2=0.88	0.643

*significant

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Table 2 Comparison between the studied groups regarding endometrial thickness and Number of mature follicles

	Groups			Test of sig	P value	Post hoc test
	CC[1] (No.=62)	Tamox[2] (No.=61)	Letrozol[3] (No.=62)			
	Mean±SD	Mean±SD	Mean±SD			
Basic ET (mm)	2.70 ±0.68	2.64 ±0.67	2.62 ±0.73	Kruskal-Wallis=0.77	0.679	1vs. 2=0.530 1 vs.3=0.407 2vs.3=0.783
Preovulatory ET (mm)	7.52 ±0.90	9.38 ±1.68	9.44 ±1.84	F=31.14	<0.001*	1vs. 2& 3<0.001 2vs.3=0.927
No of follicles (Mean ±SD)	1.54 ±0.89	1.22 ±0.69	1.08 ±0.55	Kruskal-Wallis=11.56	0.003*	1vs. 2=0.037* 1 vs.3=0.001* 2vs.3=0.208

*significant

Table 3 Comparison between the studied groups regarding their clinical pregnancy rate and midluteal serum progesterone

	Groups						Test of sig	P value	Post hoc test
	CC1 (No.=62)		Tamox2 (No.=61)		Letrozol3 (No.=62)				
Clinical pregnancy rate (No & %)	16	25.8	21	34.4	25	40.3	χ^2=2.96	0.227	-
Mid-luteal serum progesterone(Mean ±SD)	22.69 ±9.97		29.16 ±12.28		28.08 ±11.35		Kruskal-Wallis=14.11	<0.001*	1vs. 2=0.001* 1 vs.3=0.001* 2vs.3=0.689

*significant

Discussion

There was no significant difference between the 3 groups regarding, duration of infertility and the presence of obesity. Also, basic endometrial thickness was not significantly different between the 3 groups. The current study shows a statistically significant difference between clomiphene citrate group in one side and both tamoxifen and letrozole in the other side regarding preovulatory endometrial thickness being thinner in group 1 (CC) than other two groups, group 2 (letrozole) and group 3 (TMX).Although the mean number of mature follicles was significantly more in group 1in comparison to the other 2 groups, clinical pregnancy rate was higher in group 2 and 3 than in group 1and not reaching statistical significance between them. Again mid luteal serum progesterone was significantly higher in group 2 and 3 than in group 1.

El Sedeek & El maghra by studied 124 anovulatory patients, divided into two groups (CC and letrozole), the mean endometrial thickness was higher in letrozole group 8.3mm more than CC group which was 7.2mm with follicles number which is higher in CC group than letrozole group. Ovulation rate which was higher in letrozole group 69.5% than CC of 4%, pregnancy rate was higher in letrozole group 33% than CC group 28%.[14]

On the other hand the results of the current study disagree with Kar et al.[15] who included 103 anovulatory patients, divided into two groups CC and letrozole, mean endometrial thickness was almost the same between the two groups CC 7.6mm and letrozole 7.65mm with higher number of follicle in CC than letrozole, ovulation rate was higher in letrozole group 73.08% than CC group 60.78% pregnancy rate significantly higher in letrozole than CC group.[15] Another study conducted in 2009 did not found significant difference in endometrial thickness between CC and letrozole. And those 2 studies compared only letrozole to CC not including tamoxifen.[16]

Roy et al.[17] were in agreement with the current study, it included 204 ovulatory patients divided in to two groups (CC and letrozole). The results were number of follicles were higher in CC group than letrozole group, ovulation rate was almost of no difference in CC group 67.9% and letrozole group 66.6% pregnancy rate was significantly higher in letrozole group 43.8% than CC 26.4% mean endometrial thickness was significantly higher in letrozole group 9.1mm than CC group 6.3mm.[17]

In study of Selim and Borg, which included 200 an ovulatory PCOS patients divided into two groups (CC and letrozole) the results were ovulation rate which was slightly higher in letrozole group 70.6% than CC group 64.6% pregnancy rate was slightly higher in letrozolegoup 28.4% than CC group 20.2%, mean endometrial thickness was higher in letrozole group 9.9mm than CC group 7.7mm.[18]

Pant, 2013 included 200 anovulatory patients divided into 2 groups (CC and TMX), the results were ovulation rate (65% and 63% respectively), pregnancy rate (13.6% and 17.4% respectively),

these results shows no significant difference between the two groups. Endometrial thickness shows significant difference which is thicker in TMX group > 8mm and CC < 8mm, corresponding with the results of the current study.[19]

Also in agreement with, Hussain et al.[20] who included 150 an ovulatory patients, divided into two groups (CC and letrozole). The results were number of follicles were higher in CC than letrozole, ovulation rate was significantly higher in CC than letrozole, pregnancy rate was higher in letrozole group 25.3% than CC group 16% mean endometrial thickness was higher in letrozole group 9.2 mm than CC group 8.4mm and this study didn't include tamoxifen.[20]

El Khateeb & Mahran show agreement with the current study, that trial included 200 infertile women PCOS defined according to Revised Rotterdam criteria divided into two groups letrozole and clomiphene citrate, endometrial thickness was highly significant in letrozole group (10.1mm) than CC group (8.02mm) ovulation was not statistically significant. Clinical pregnancy rate was significant higher in letrozole 14.8% than CC group 10.4% without no ovarian hyper stimulation syndrome in either groups.[21]

A recent study, 2016, conducted on 150 PCOS patients divided into three groups CC, TMX and letrozole agree with the current study regarding endometrial thickness. Regarding ovulation and clinical pregnancy rates, the results were not correlating, this study showing significantly thinner endometrium in CC group compared with the other two groups, with statistically non significant difference in either ovulation or pregnancy rates.[3]

Conclusion

In the current study, although the mean number of follicles is more with CC, the endometrial thickness, mid luteal serum progesterone and clinical pregnancy rate are more with tamoxifen and letrozole. Being nonsignificant difference between tamoxifen and letrozole groups regarding last parameters, the authors recommend that tamoxifen, being cheeper than letrozole, should be the first choice to induce ovulation in anovulatory PCO women.

Inability to conduct a randomized controlled trial constitutes unintended limitation of the study. A multicenter randomized controlled trial is required in future research to draw a firm conclusion.

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Conflicts of interest

The authors certify that no actual or potential conflicts of interest in relation to this article exist.

Author contribution

Elsayed Elshamy: project development, data collection manuscript writing.

Mohammed Khalafallah: project development, manuscript writing and revision.

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