RESULTS

Sixty infertile women were selected from patients attending out patient clinic in Benha University hospital from December 2007 to February 2010. All patients were diagnosed as having PCOS according to Rotterdam criteria ***(Costello, 2005).***

In this prospective randomized comparative study, after a written consent had been taken 60 infertile patients were divided randomly into 2 groups (A & B) according to attendance, odd numbers group (A) and even numbers group (B). In group (A), (n=30) letrozole ***(Femara; Novartis, East Hanover, NJ)*** was given orally in a dose of 5 mg/day for 5 days starting from the third day of a spontaneous or progesterone induced menstrual bleeding. Medroxyprogesterone acetate ***(Provera; Pharmacia & Upjohn)*** was prescribed 10 mg/day for 5 days to induce withdrawal bleeding in the amenorrheic patients. In group (B) (n=30) Clomiphene citrate ***(Clomid; Aventis Pharma, France)*** was given in a dose 100 mg/day instead of letrozole. This regimen was repeated in 2 groups up to 6 cycles unless pregnancy occurs.

All data are collected and summarized using percentages, means and standard deviation using a statistical computer package for social sciences ***(SPSS version 9.0, Chicago IL, USA).***

Comparison of means were done using a ***student*** t-test. Comparison of percentage were done using the ***chi- square*** x^2 test with ***fisher's*** test when the ***chi-square*** test requirement were not fulfilled. The threshold of significance was fixed at p-value < 0.05.

Table (1): Clinico-epidemiological data of study population.

	Group (I) Letrozole (n=30)			Group (II) Clomiphene citrate (n=30)			t-test	P value
	Range	**Mean**	**SD**	**Range**	**Mean**	**SD**		
Age (years)	18-33	24.12	3.24	19-35	24.61	4.15	1.620	0.110(NS)
Weight (kg)	49.5:93	68.34	18.71	46:95	69.51	19.12	1.781	0.113 (NS)
Heigh (meter)	1.51:1.74	1.63	0.105	1.48:1.77	1.66	0.101	1.801	0.078 (NS)
BMI (kg/m^2)	19.68 35.84	26.98	4.54	18.86-33.75	25.00	4.31	1.817	0.074(NS)
Period of Infertility (years)	2-13	5.54	2.74	2-15	5.94	3.41	1.838	0.071(NS)

SD: standard deviation, NS: not significant

The characteristics of the study population is Shown in **table (1).** There was no statistically significant difference in any clinics-epidemiological characters among women of group I and II.

Table (2): The relative incidence of clinical signs of PCOS among studied groups.

	Group I (letrozole) "n=30"		**Group II (cc) "n=30"**	
	n.	%	n.	%
Oligomenorrhea	19	63.3	18	60.0
X^2 P	0.73 0.45 N.S			
Hirsutism	16	53.3	18	60.0
X^2 P	0.69 0.41 N.S			
Obesity (BMI>25)	15	50.0	14	46.7
X^2 P	0.68 0.42 N.S			
Positive US Criteria	21	70.0	22	73.3
X^2 P	0.74 0.36 N.S			

X^2 = chai – square test N.S = not significant

The relative incidence, of clinical signs of PCOS among studied groups is shown in **table (3)** the overall incidence of oligomenorrhea, hirsutism, obesity, and positive ultrasound criteria were 61.7%, 56.7%, 48.3% and 71.7%. There was no statistically significant difference in the relative incidence of oligomenorrhea, hirsutism, obesity and positive US criteria among women of group I and II.

Table (3): Biochemical data of study population

	Group (I) Letrozole (n=30)			Group (II) Clomiphene citrate (n=30)			t-test	P value
	Range	Mean	SD	Range	Mean	SD		
FSH (mIU/mL)	3.21-9.42	6.67	1.85	3.38-9.56	7.10	1.85	0.967	0.337(NS)
LH (mIU/L)	9.42-19.4	14.92	4.21	9.43-19.30	14.45	3.87	1.537	0.129(NS)
LH/FSH	0.79-5.38	2.01	1.23	0.70-5.82	2.13	1.21	0.429	0.669(NS)
Fasting blood glucose (mg/dl)	74:115	84.11	14.13	72:112	87.13	13.91	1.23	0.102 (NS)
Insulin IU/mL	10.4 2319	16.49	4.37	10.24-28.71	15.94	5.20	0.972	0.335(NS)
Testostreone (nmol/L)	1.51:3.84	2.81	1.01	1.49:3.87	2.83	1.02	0.998	0.541 (NS)
DHEA-S µg/dl	195.281	229	31.17	199-279	231	25.5	0.518	0.115 (NS)

SD: standard deviation, NS: not significant

The characteristics of the study population is Shown in **table (3).** There was no statistically significant difference in any investigations among women of group I and II.

Table (4): Distribution of study population according to age, BMI and duration of infertility.

	Group I n=30	Group II n=30	Total n=60	%
age (years)				
18-24y	12	11	23	38.33
>24-30	14	15	29	48.33
>30-35	4	4	8	13.33
Total (n)	**30**	**30**	**60**	
BMI kg/m^2				
18-25	4	3	7	11.67
>25-30	18	20	38	63.33
≥ 30-36	8	7	15	25
Total (n)	**30**	**30**	**60**	
Duration of infertility (years)				
2-5	19	18	37	61.67
>5-10	8	8	16	26.67
>10-15	3	4	7	11.66
Total (n)	**30**	**30**	**60**	

Table (4) Shows that:

- Distribution of study population showed that nealry 1/2 of cases were aged (>24 -30 y) and 38.33% were aged (18-24 y).
- The table shows that 63.33% of cases had BMI (>25-30 kg/m^2) and 25% had BMI (>30-36kg/m^2).
- The table also shows that 61.67% of cases had 1ry infertility (2-5y) and 26.67% of cases had 1ry infertility (>5-10y).

Table (5): The number of follicles ≥ 18 mm in diameter and endometrial thickness in each group on day of hCG administration.

	Group I (letrozole) "n=30"	**Group II (CC) "n=30"**
No. of follicles ≥ 18 mm		
Range	1.0-5.0	1.0.3.0
Mean	2.2	1.5
S.D.	1.18	0.77
F	35.13	
P	0.00001**(S)	
Endometrial Thickness (mm)		
Range	6.0-14.0	4.0 – 9.0
Mean	8.86	5.56
S.D.	2.37	1.61
F	78.7	
P	0.0001**(S)	

**** Highly significant**

Table (5). The number of follicles ≥ 18 mm in diameter and endometrial thickness in each group on day of hCG administration was significanlty higher in letrozole group compared to CC group.

Table (6): Effect of age on number of follicles ≥18 mm. on day of hCG administration

Age (years)	Group (I)			Group (II)			P value
	Range	Mean	SD	Range	Mean	SD	
(a) 18-24	1.5	2.78	1.87	1:3	1.8	0.87	<0.01 (S)
(b) > 24-30	1.5	2.45	1.65	1:3	1.71	0.81	<0.01 (S)
(c) >30-35	1-3	1.78	0.73	1:2	1.48	0.41	>0.05 (NS)
P value (a-b)	(NS) >0.05			(NS) >0.05			
P value (a-c)	(S) <0.01			(S) <0.01			
P value (b-c)	(S) <0.05			(S) < 0.05			

Table (6) shows that:

- Ovulatory response was signficantly better in letrozole group compared to CC group in age group (18-24y) & (>24-30y) but no statistically significant difference in age group (>30-35y).
- In Both groups: ovulatory response was significantly lower in age group (>30-35y) compared to groups (18-24y) & (>24-30y) with no significant difference between age gorup (18-24y) and (>24-30y).

Table (7): Effects of BMI on number of follicles ≥18 mm on day of hCG administration

BMI kg/m^2	Group (I)			Group (II)			P value
	Range	Mean	SD	Range	Mean	SD	
(a) 18-25	1:5	2.92	1.87	1:3	1.78	0.77	>0.05(NS)
(B) > 25-30	1:5	2.87	±1.84	1:3	1.72	0.87	<0.05 (S)
(c) >30-36	1:3	1.58	0.79	1:2	1.45	0.38	>0.05 (NS)
P value (a-b)	(NS) >0.05			(NS) >0.05			
P value (a-c)	(S) <0.05			(S) <0.01			
P value (b-c)	(S) <0.01			(S) < 0.05			

Table (7) showes that:

- Ovulatory response was significantly better in letrozole group compared to CC group in BMI group (>25:30 kg/m^2**)** with no significant difference in BMI groups (18-25 kg/m^2**)** and (>30-36 kg/m^2**).**

- In Both groups ovulatory response was significantly lower in BMI group (>30-36 kg/ m^2) compared to groups (18-25 kg/m^2) and (>25-30 kg/m^2) with no significant difference between group (18-25 kg/m^2) and (>25-30 kg/m^2).

Table (8): Effect of duration of infertility on number follicles ≥18 mm on day of hCG administration

Duration of infertility (years)	Group (I)			Group (II)			P value
	Range	Mean	SD	Range	Mean	SD	
(a) 2-5	1:5	2.41	1.38	1:3	1.67	0.63	<0.05 (S)
(b) > 5-10	1:5	2.16	1.09	1:2	1.51	0.43	<0.05 (S)
(c) > 10-15	1:3	1.37	0.24	1:2	1.38	0.31	>0.05 (NS)
P value (a-b)	(NS) >0.05			(NS) >0.05			
P value (a-c)	(S) <0.01			(S) <0.05			
P value (b-c)	(S) <0.05			(NS) < 0.05			

Table (8) shows that:

- Ovulatory response was significantly better in letrozole group compared to CC group in infertile cases (2-10y) with no significat diffrence in infertile cases (>10-15y).
- In letrozole gorup ovulatory response was significantly lower in infertile cases (>10-15y) compared to those (2-10y) with no significant difference between infertile cases (2-5y) and those (>5-10y).
- In CC group infertile cases (2-5y) was significantly better than group (>10-15 y) with no other significant differences.

Table (9): Effect of age on endomterial thickness (mm) on day of hCG administration.

Age (years)	Group (I)			Group (II)			P value
	Range	Mean	SD	Range	Mean	SD	
(a) 18-24	8-14	10.2	2.06	5-9	7.04	1.58	<0.001 (S)
(b) > 24-30	6-14	8.41	2.35	4-9	6.03	1.82	<0.005 (S)
(c) > 30-35	6-12	7.91	1.82	4-9	5.78	1.26	< 0.05 (S)
P value (a-b)	(S) <0.05			(NS) >0.05			
P value (a-c)	(S) <0.01			(S) <0.05			
P value (b-c)	(N.S) >0.05			(NS) > 0.05			

Table (9) shows that:

- Endometrial thickness on day of hCG administration was significantly better in letrozole groups compared to CC group in all age subgroups.
- In letrozole group patietns aged (18-24y) were significantly better than those (>24-35y) and no significant difference was found between patients aged (>24-30y) and those (>30-35y).
- In CC group patients aged (18-24y) were significantly better than those (>30-35 y) with no other significant difference.

Table (10): Effect of BMI on endometrial thickness (mm) on day of hCG administration

BMI kg/m^2	Group (I)			Group (II)			P value
	Range	Mean	SD	Range	Mean	SD	
(a) 18-25	8-14	10.64	2:31	5-9	6.87	1.32	<0.05 (S)
(B) > 25-30	8-14	10.51	1.42	5-9	5.41	0.87	< 0.01 (S)
(c) > 30-36	7-12	8.81	1.79	4-9	5.31	1.24	< 0.05 (S)
P value (a-b)	(NS) >0.05			(NS) >0.05			
P value (a-c)	(S) <0.05			(S) <0.05			
P value (b-c)	(S) <0.05			(NS) >0.05			

Table (10) shows that:

- Endometrial thickness on day of hCG adminstration was significantly better in letrozole than CC groups in all BMI subgroups.
- In letrozole group patietns with BMI (18-30 kg/m^2) were significantly better than those (>30-36 kg/m^2) with no significant difference between subgroups (18-25 kg/m^2) and (>25-30 kg/m^2).
- In CC group patients with BMI (18-25 kg/m^2) were significantly better than those (>30-36 kg/m^2) with no other significant differences.

Table (11): Effect of duration of infertility on endometrial thickness (mm) on day of hCG administration

Duration of infertility (y)	Group (I)			Group (II)			P value
	Range	Mean	SD	Range	Mean	SD	
(a) 2-5	8-14	10.1	2.87	5-9	7.11	1.83	<0.01 (S)
(b) >5-10	7-14	4.12	2.06	4-9	6.53	1.58	<0.01 (S)
(c) >10-15	7-10	8.67	1.54	5-8	6.02	0.89	<0.05 (S)
P value (a-b)	(NS) >0.05			(NS) >0.05			
P value (a-c)	(S) <0.05			(S) <0.05			
P value (b-c)	(NS) >0.05			(NS) >0.05			

Table (11) Shows that:

- Endometrial thickness on day of hCG adminstration was significantly better in letrozole than CC group in all cases regardless duration of infertility.
- In Both groups patietns with duration of infertility (2-5y) were significantly better than those (>10-15y) with no other significant differences.

Table (12): The mean duration (days) till hCG injection in group I,II.

	Group I (Letrozole) "n=30"	Group II (CC) "n=30"
Day of cycle on hCG Injection		
Range	12.0 – 17.0	13.0-17.0
Mean	14.7	15.3
S.D.	1.62	1.207
t	3.65	
P	0.12	

The mean duration needed to reach follicular maturity and to give hCG injection among different groups is shown in **table (12).** Follicular maturity was achieved in a relatively shorter period among women of group I than those of group II. However, this difference was proved to be statistically not significant.

Table (13): Ovulatory response to letrozoe & C.C.

	Group I Letrozoe (n = 30)		Group II CC=30		X^2	P
Ovulation	n.	%	n.	%	4.591	0.03*
	26	86.6	18	60		

Table (13): Shows the ovulatory response among women of the study groups there was statistically significant differences between group I & group II (P. value = 0.03).

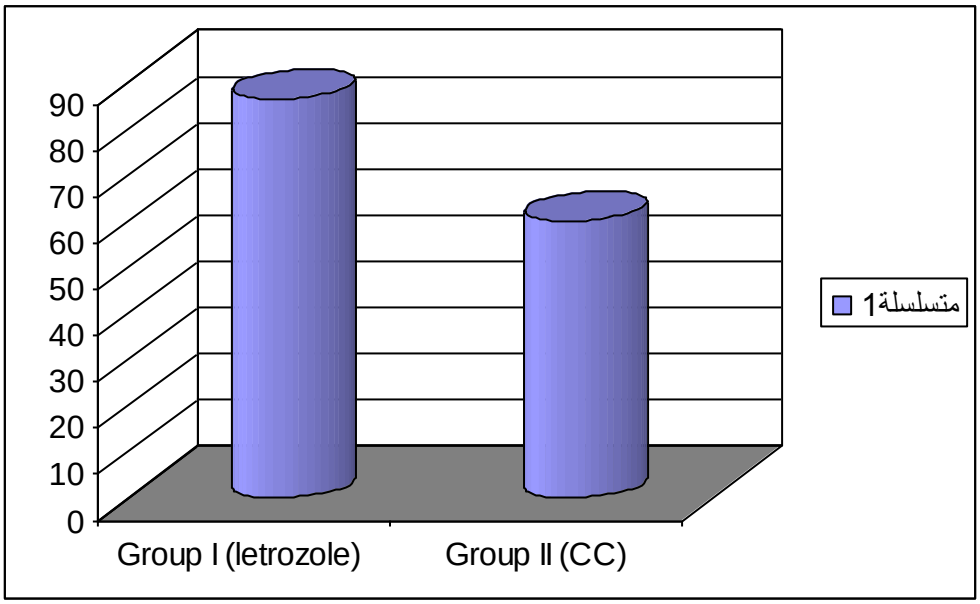

Fig. (9): Ovulatory response to letrozoe & C.C

Table (14): The number of recorded pregnancies in group I, II

	Group I (Letrozole) "n=30"		Group II (CC) "n=30"	
	n.	**%**	**n.**	**%**
Preg.	11	36.7	5	16.7
X^2	6.79			
P	0.02*			
Total n. of cycles	152		156	
% of preg./cycle	7.2		3.2	
X^2	4.87			
P	0.03*			

The number of recorded pregnancy in each group is shown in **table (14).** There was highly significant number of pregnancies as evidenced by positive pregnancy test and intrauterine gestational sacs in group I than group II (11 cases or 36.7% versus 5 cases or 16.7% respectively). The difference between group I & II was statistically significant also rate of pregnancy per cycle was (7.2 % versus 3.2%) the difference was also statistically significant.

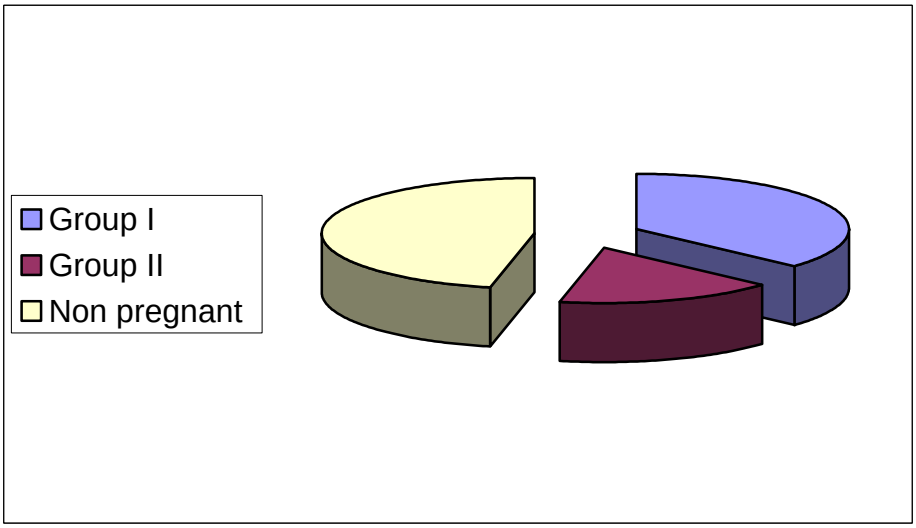

Fig. (10): Incidence of pregnancy in two groups

Table (15): Effect of age on pregnancy rate

Age (years)	Group (I)		Group (II)		P value
	n	%	n	%	
a) 18-24	7	58.3	4	36.4	<0.05 (S)
b) >24-30	4	28.7	1	6.7	<0.01 (S)
c) >30-35	-	-	-	-	NS
P value (a-b)	(S) <0.05		(S) <0.01		
P value (a-c)	(S) <0.01		(S) <0.01		
P value (b-c)	(S) <0.01		(S) <0.01		

Table (15) shows that:

- Pregnancy rate was significantly better in letrozole than CC group regardless the patients age.
- In both groups, patietns aged (18-24y) were significantly better than those (>24 y) and patients aged (>24-30y) were significantly better than those (>30-35y).

Table (16) Effect of BMI on pregnancy rate

BMI (kg/m^2)	Group (I)		Group (II)		P value
	n	%	n	%	
a) 18-25	3	75%	1	33.3	<0.05(S)
b) >25-30	7	38.9%	3	15	<0.05 (S)
c) >30-36	1	12.5%	1	14.2	>0.05 (NS)
P value (a-b)	(S) <0.05		(S) <0.05		
P value (a-c)	(S) <0.01		(S) <0.05		
P value (b-c)	(S) <0.05		(NS) >0.05		

Table (16) Shows that:

- Pregnancy rate was signficantly better in letrozole than CC groups in patients with BMI (18-30 kg/m^2) with no significant difference in cases with BMI (>30-36 kg/m^2).
- In letrozole group, patients with BMI (18-25 kg/m^2) were significantly better than those (>25-30 kg/m^2) and those (>25-30 kg/m^2) were significantly better than those (>30-36 kg/m^2).
- In CC group patients with BMI (18-25 kg/m^2) were significantly better than those (>25-36 kg/m2) with no other significant differences.

Table (17): Effect of duration of infertility on pregnancy rate

Duration of infertility (years)	Group (I)		Group (II)		P value
	n	**%**	**n**	**%**	
a) 2-5	8	42.1%	4	22.2	<0.05(S)
b) >5-10	3	37.5%	1	12.5	<0.05 (S)
c) >10-15	-	-	-	-	(NS)
P value (a-b)	(NS) >0.05		(S) <0.05		
P value (a-c)	(S) <0.01		(S) <0.01		
P value (b-c)	(S) <0.01		(S) <0.01		

Table (17) shows that:

- Pregnancy rate was significantly better in letrozole than CC group in patients with duration of infertility (2-10y) with no pregnacy at all in infertile cases (>10-15y).

- In letrozole group infertile cases (2-10y) were significantly better than those (>10-15 y), with no other significant differences.

- In CC group infertile cases (2-5y) were significantly better than those (>5-15y) and those (5-10y) were significantly better than those (>10-15y).

Table (18): Comparison of patients characters in pregnant and non pregnant groups:

Character	Pregnant group (n=16)	Non pregnant group (n=44)	P value
Wife			>0.05
Mean age ± SD (y)	24.7 ± 3.65	24.9 ± 4.16	N.S
Range (y)	18-34	18-35	
Husband			
Mean age ± SD (y)	32.8 ± 4.43	33.6 ± 6.86	>0.05
Range (y)	26-39.16	25-41.16	N.S
Infertility			>0.05
Mean duration ± SD (y)	5.15 ±1.23	5.98 ± 1.26	N.S
Range (y)	3-6	2-15	

Table (18): Compares the characters of pregnant with that of non pregnant cases. There was no significant difference as regard wife age, husband age or duration of infertility.

Table (19): Comparison of sperm characters in pregnant and non pregnant cycles.

Character	Pregnant group (n=16)	Non pregnant group (n=44)	P value
Sperm Concentration / ml (Mean ± SD).	61.88 ± 9.57 $X10^6$	66 ± 10.87 X 10^6	> 0.05 N.S
Sperm motility: (Mean ± SD)	52.33 ± 8.66%	51.02 ±9.44%	>0.05 N.S
Total Number of Sperms: (Mean ± SD)	184.87 ± 22.37 $X10^6$	193.12 ± 24.27 X 10^6	>0.05 N.S

Table (19): No significant difference was found between pregnant and non pregnant groups.

Table (20): Early outcome of pregnancy by TV.US

Outcome	n.	%
Single	15	93.7%
Twins	"with CC"	6.3%
Triplet	0	00%
Ectopic pregnancy	0	00%
Blighted ovum	0	00%

Table (10): shows the early outcome of pregnancy by TV. US 93.7% was singleton, 6.3% was twin pregnancy in CC group & no triplets, ectopic pregnancy or Blighted ovum.

Table (21): Incidence of side effects to letrozole and CC between women of group I and II.

	Group I (Letrozole) "n=30"		**Group II (CC) "n=30"**	
	n.	**%**	**n.**	**%**
Headache	2	6.6	2	6.6
Nausea	2	6.6	1	3.3
Peripheral edema	1	3.3	0	0.0
Fatigue	1	3.3	1	3.3
Hot flushes	3	10.0	2	6.6
Bone and back pain	2	6.6	1	3.3
Rash	1	3.3	2	6.6
Ovarian Hyper stimulation syndrome	0	00%	0	00%
X^2	1.81			
P	0.93 (N.S)			

Comparison of the side effects of letrozole and CC showed that both drugs are generally tolerated with no significant differences in the relative incidence of side effects (P=0.93).