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Original Research Article

Coenzyme q10 and letrozole versus letrozole alone for ovulation induction in polycystic ovary syndrome

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is the largest single cause of anovulatory infertility. PCOS is associated with oxidative stress. Coenzyme q10 (Coq10) is an antioxidant that protects the mitochondria from damage caused by either insulin resistance or oxidative free radicals. The objective of the study was to compare the effect of combined Coq10 and letrozole than of letrozole alone for ovulation induction in women with PCOS.
Methods: This open label parallel design randomized controlled trial study was conducted on 80 infertile women with PCOS selected for ovulation induction. Eligible women were randomized either to combined Coq10 and letrozole (40 patients, 83 cycles) or letrozole alone (38 patients, 91 cycles). The outcome measures were mature follicles, adequate endometrial thickness, ovulation and pregnancy.
Results: Mature follicles (≥18-25 mm) were significantly higher in women given Coq10 at 2nd (74.2% vs 31.3%) and 3rd cycles (83.3% vs 28.6%). Adequate endometrial thickness was significantly higher in women given Coq10 in second (90.3% vs 56.3%) and third cycle (94.4% vs 47.6%). When Coq10 was added to letrozole, ovulation rates were significantly higher (87.1% vs 53.1% in second cycle), (83.3% vs 38.1%, in third cycle). Cumulative pregnancy was 2.37 times (95% CI 1.03-5.48) higher in women having Coq10 in addition to letrozole for ovulation induction.
Conclusions: Coq10, as an adjuvant to ovulation induction with letrozole improves ovarian response, ovulation and pregnancy in PCOS women. Combination of Coq10 and letrozole can be tried successfully before a more complicated and expensive treatment such as gonadotrophins and laparoscopic ovarian drilling.

Keywords: PCOS, Coenzyme q10, Letrozole, Oxidative stress, Ovarian response

INTRODUCTION

Polycystic ovary syndrome (PCOS), commonly known as PCOS is the largest single cause of anovulatory infertility.[1] Rezvanfar and colleagues demonstrated that oxidative stress has critical role in the pathogenesis of PCOS.[2] PCOS is reported to be associated with mitochondrial dysfunction which has a negative impact on oocyte quality, compromising meiotic spindle configuration and chromosomal misalignment and eventually causing oocyte death.[3] Coenzyme q10 (Coq10) also known as ubiquinone is a mitochondrial antioxidant, a substance that protects the mitochondria from damage caused by either insulin resistance or oxidative free radicals.[4] Coq10 supplementation improves human oocyte quality and subsequent reproductive performance by its role in ATP synthesis and mitochondrial protection from ROS (reactive oxygen species) oxidative damage. Letrozole, an aromatase inhibitor has been recommended as the first line drug for induction of ovulation in anovulatory infertility in terms of mono-follicular ovulation, better endometrial thickness and absence of lag endometrium.[1]Letrozole decreases the secretion of estrogen and causes an increase

in gonadotropins, which in turn causes maturation of the ovarian follicles.

In Bangladesh where early marriage is prevalent, a major contributory cause of infertility in young women is PCOS. About 20-25% of PCOS women fail to ovulate with incremental doses of ovulation inducing drug such as clomiphene citrate or letrozole. Ovulation induction with gonadotrophins is the treatment for these women. Sometimes they need laparoscopic ovarian drilling which becomes a burden for many poor patients of our country. In this context, administration of Coq10 along with letrozole may be helpful for infertile women with PCOS resulting in more mature follicles and pregnancy, thus ameliorating the extra expense for gonadotropin injection or need for repeated cycles of ovulation induction. Side effects of Coq10 is minimum, so can be taken easily.

New drugs and new concepts are introduced day by day as ovulation physiology is understood by infertility specialists. There is paucity of data on oxidative stress and antioxidant supplementation in patients with PCOS. In this context, Coq10 as an antioxidant in PCOS patients along with ovulation induction drug like letrozole may be explored in the anovulatory and infertile PCOS women. No relevant study of antioxidants with letrozole was found in PCOS women. This study was designed to evaluate the effectiveness of Coq10 along with letrozole as ovulation inducing drug.

METHODS

This was an open label parallel design randomized controlled trial carried out in the Department of Reproductive Endocrinology and Infertility of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from February 2021 to January 2022. The participants were PCOS women (diagnosed according to Rotterdam criteria), age range 18-35 years, with infertility for 1 year or more and selected for ovulation induction. The exclusion criteria were body mass index (BMI) less than 18 kg/m^2 and more than 30 kg/m^2, male factor infertility, female factors other than anovulation (bilateral tubal block, endometriosis), medical disease (impaired glucose tolerance, diabetes mellitus, hypertension, kidney disease), taking drugs (metformin, inositol) and antioxidants in previous three months and hypersensitivity to Coq10. The study was approved by institutional review board. Informed consent was taken from each participant.

The participants were randomized into experimental and comparator groups. The experimental group A was given Coq10 (cap Ubi-Q, 100 mg cap, Radiant Pharmaceuticals Limited, Dhaka) twice daily for 3 cycles along with letrozol (Tab Letrol, Renata Pharmaceuticals limited, Dhaka) daily from day 2 to 6 of menses. The comparator group B was given only letrozole, 5 mg daily from day 2 to 6 of menses for 3 cycles. All participants were instructed not to take any medications during the trial without consultation with primary investigator. Primary outcome variables were ovarian response and ovulation. Ovarian response was measured by transvaginal sonography on Day 12-14 by the presence of mature follicle and adequate endometrial thickness. Ovulation was measured by mid-luteal progesterone (>3 ng/ml). Secondary outcome was pregnancy ovarian response (i.e., mature follicles and endometrial thickness) was assessed by folliculometry using transvaginal probe (Mindray DP-2200 plus ultrasound system). The folliculometry was carried out in both groups on day 12-14 of the stimulation cycle. The HCG injection (Inj HCG of Popular Pharmaceuticals Limited, Dhaka) 5,000 IU was given intramuscularly when at least one follicle became mature (18 - 25 mm). Timed intercourse was advised. Confirmation of ovulation was done by mid-luteal (7 days after Inj HCG) serum progesterone (>3 ng/ml) measured using chemiluminescent immunoassay [SEIMENS ADVIA centaur Xp Immunoassay system].

PCOS was diagnosed on the basis of revised 2003 Rotterdam criteria, which require two of the following three: oligo and /or anovulation (defined as delayed menses >35 days or <8 spontaneous menstruation/year), clinical hyperandrogenism (hirsutism using modified Ferriman-Gallway score of ≥ 8), polycystic ovarian morphology on ultrasonography ≥ 12 follicles in each ovary measuring 2-9 mm in diameter and / or increased ovarian volume >10 cm^3. Mean follicular diameter was measured by taking the mean of two internal diameters of each follicle. In our study, follicle measuring 14-17 mm detected on day 12-14 folliculometry by a 6.5 MHz transvaginal (TVS) was regarded as developing follicles. Mature follicle was determined by folliculometry done on day 12-14 by transvaginal sonography. Mean size of mature follicle was considered between 18 to 25 mm. Endometrial thickness (ET) was measured at the greatest diameter perpendicular to the mid sagittal plane in the fundal region on day 12-14 by transvaginal sonography. The ET measuring ≥7 mm was considered optimum for ovulation. Ovulation was diagnosed when mid-luteal serum progesterone was >3 ng/ml at the follow up visit. Pregnancy was determined after missed period by urinary pregnancy test. Clinical pregnancy was confirmed by USG at 6-7 weeks.

Random sequence generation was done by computer generated random numbers. Permuted block randomization was done with stratification for BMI. Random allocation of treatment was done by someone not involved with the care of the patients. Allocation concealment was done by sequentially numbered sealed opaque envelops; each had a card inside labeled with an alphabet representing the intervention type. Allocation was never changed after opening the closed envelops. All data were collected by the principle investigator. There was no blinding.

Sample size of participants was calculated as 40 in each group, for a power of 0.80, a significance level of 0.05 and

an effect size of 1.67. Statistical analyses were carried out by the SPSS program for windows, version 22.0 (SPSS, Chicago, IL). The data were tested for homogeneity prior to analysis. The mean±SD values or median, interquartile range were calculated as appropriate for outcome variables. Data was tested using the parametric tests such as unpaired t test, paired t-test, non-parametric test as Mann Whitney U test and Chi square test as appropriate. P<0.05 was considered as statistically significant.

RESULTS

This randomized controlled trial was conducted in the Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib medical university, Dhaka from February 2021 to January 2022. Initially eighty PCOS women selected for ovulation induction were randomized into intervention (Coq10 plus letrozole) and comparator (letrozole only) group. The attrition in participants for various reasons (pregnancy and drop out) in different ovulation induction cycles are shown in the Table 1.

Table 2-4 describes the socio-demographic, clinical and laboratory parameters of study participants and shows that the two groups have no significant difference. Table 5-7 compares the two groups regarding ovarian response in terms of the presence of mature follicle and favorable endometrium and ovulation. Women given Coq10 in addition to letrozole were more likely to have mature follicle than those given letrozole only for ovulation induction and in the 2nd and 3rd cycle the chances were more than double. The adequate endometrial thickness was more likely in group A receiving Coq10. Ovulation rate as measured by luteal phase progesterone was higher in group A in comparison to group B in 1st cycle. In 3rd cycle ovulation rate was more than double in group A compared to group B which was statistically significant.

Table 8 compares the pregnancy rate between two groups. The pregnancy was more than double in all cycles among those who received Coq10 with letrozole. Cumulative pregnancy rate was 2.37 times higher in Coq10 and letrozole group than in letrozole only group. The difference was statistically significant (p<0.05).

Table 1: Sequence of tasks and attrition at different cycles.

Randomized, (n=80)	
Allocated to intervention (Combined Coq10 and letrozole), (n=40)	Allocated to intervention (Letrozole only), (n=40)
Received allocated intervention, (n=40)	Received allocated intervention, (n=38)
(Combined Coq10 and letrozole) **First cycle, (n=40) and analyzed, (n=40)**	(Letrozole only) First cycle, (n=38) and analyzed, (n=38)
Lost to follow up, (n=2) **Discontinued intervention due to pregnancy, (n=7)**	Lost to follow up, (n=3) Discontinued intervention due to pregnancy, (n=3)
(Combined Coq10 and letrozole) **Second cycle, (n=31) and analyzed, (n=31)**	(Letrozole only) Second cycle, (n=32) and analyzed (n=32)
Lost to follow up, (n=9) **Discontinued intervention due to pregnancy (n=4)**	Lost to follow up, (n=10) Discontinued intervention due to pregnancy, (n=1)
(Combined Coq10 and letrozole) **Third cycle, (n=18) and analyzed, (n=18)**	(Letrozole only) Third cycle, (n=21) and analyzed, (n=21)
Pregnancy, (n=4)	Pregnancy, (n=2)

Table 2: Socio-demographic characteristics of the study participants.

Parameters	**Group A (Coq10, letrozole), (n=40)**		**Group B (Letrozole only), (n=38)**		**P value**
	N	%	N	%	
Age (years)					
18-21	12	30.0	7	18.4	0.391
22-25	12	30.0	21	55.3	
26-29	8	20.0	5	13.2	
30-35	8	20.0	5	13.2	
Mean±SD	24.75±4.2		23.74±5.0		
BMI (kg/ m)					
18-23.4	8	20.0	11	28.9	0.158
23.5-27.4	16	40.0	16	42.1	
27.5-30	16	40.0	11	28.9	
Mean±SD	26.06±2.808		25.22±2.655		
Infertility					
Primary	32	80.0	31	81.6	0.544
Secondary	8	20.0	7	18.4	

Continued.

Parameters	Group A (Coq10, letrozole), (n=40)		Group A (Coq10, letrozole), (n=40)		P value
	N	%	N	%	
Occupational status					
Housewife	29	72.5	32	84.2	0.197
Service holder	5	12.5	2	5.3	
Student	6	15.0	4	10.5	
Monthly income (BDT)					
10,000-20,000	10	25.0	10	26.3	0.561
20,000-50,000	21	52.5	19	50.0	
>50,000	9	22.5	9	23.7	

ns=not significant.

Table 3: Clinical characteristics of the study participants.

Clinical characteristics	Group A (Coq10, letrozole), (n=40)		Group B (Letrozole only), (n=38)		P value
	N	%	N	%	
Oligomenorrhoea	40	100	38	100	No difference
Hirsutism	39	97.5	38	100	0.513
Acne	40	100	35	92.1	0.111
Polycystic ovaries	40	100	37	97.4	0.487

Table 4: Baseline laboratory parameters of study participants.

Laboratory parameters	Group A (Coq10, letrozole), (n=40)	Group B (Letrozole only), (n=38)	P value
Serum LH (mIU/ml)	6.242±3.374	6.937±3.808	0.714
Serum FSH (mIU/ml)	6.056±2.045	5.331±2.179	0.804
Serum TSH (mIU/ml)	2.124±0.665	1.823±0.4871	0.805
Haemoglobin (gm/dl)	12.00±1.42	12.25±1.04	0.059
Fasting blood glucose (mg/dl)	5.53±0.540	6.09±4.52	0.127
2 hours after 75 gm glucose (mg/dl)	7.10±1.31	7.09±1.30	0.883
Serum prolactin (ng/dl)*	11.76 (9.607-18.537)	14.39 (8.825-18.292)	0.753[1]

*Median, interquartile range,[1] Non parametric test.

Table 5: Presence of mature follicles compared between the two groups.

Mature follicle	Group A (Coq10, letrozole)		Group B (Letrozole only)		Risk ratio (RR)	95% CI of RR	P value
	N	%	N	%			
1st cycle	(n=40)		(n=38)				
Yes	23/40	57.5	14/38	36.8	1.56	0.95-2.55	0.075
2nd cycle	(n=31)		(n=32)				
Yes	23/31	74.2	10/32	31.3	2.37	1.36-4.13	0.001
3rd cycle	(n=18)		(n=21)				
Yes	15/18	83.3	6/21	28.6	2.92	1.44-5.91	0.001

Table 6: Presence of adequate endometrial thickness compared between groups.

Endometrial thickness (mm)	Group A (Coq10, letrozole)		Group B (Letrozole only)		Risk ratio (RR)	95% CI of RR	P value
	N	%	N	%			
1st cycle	(n=40)		(n=38)				
≥ 7 mm	25/40	62.5	14/38	36.8	1.69	1.05-2.74	0.041
2nd cycle	(n=31)		(n=32)				
≥ 7 mm	28/31	90.3	18/32	56.3	1.61	1.16-2.23	0.004
3rd cycle	(n=18)		(n=21)				
≥ 7 mm	17/18	94.4	10/21	47.6	1.65	1.12-2.43	0.011

Table 7: Comparison of ovulation rate (by mid-luteal progesterone) between the two groups.

Ovulation rate	Group A (Coq10, letrozole)		Group B (Letrozole only)		Risk ratio (RR)	95% CI of RR	P value
	N	%	N	%			
1st cycle	(n=40)		(n=38)				
Yes	29/40	72.5	18/38	47.4	1.53	1.04-2.25	0.037
2nd cycle	(n=31)		(n=32)				
Yes	27/ 31	87.1	17/32	53.1	1.64	1.15-2.33	0.005
3rd cycle	(n=18)		(n=21)				
Yes	15/18	83.3	8/21	38.1	2.12	1.22-3.92	0.008

Table 8: Comparison of pregnancy rate between two groups.

Pregnancy	Group A (Coq10, letrozole)		Group B (Letrozole only)		Risk ratio (RR)	95% CI of RR	P value
	N	%	N	%			
1st cycle	(n=40)		(n=38)				
Yes	7/40	17.5	3/38	7.9	2.22	0.62-7.95	0.312
2nd cycle	(n=31)		(n=32)				
Yes	4/31	12.9	1/32	3.1	4.13	0.49-31.42	0.196
3rd cycle	(n=18)		(n=21)				
Yes	4/18	22.2	2/21	9.5	2.33	0.48-11.29	0.387
Cumulative pregnancy rate	(n=40)		(n=38)				
Yes	15/40	37.5	6/38	15.8	2.37	1.03-5.48	0.042

DISCUSSION

The objective of the current study was to evaluate the effectiveness of Coq10 in sub fertile PCOS women during ovulation induction with letrozole. There was significant improvement of ovarian response and ovulation rate in the PCOS women having Coq10, an antioxidant supplementation in addition to letrozole during ovulation induction.

Very few studies were conducted to evaluate the effectiveness of Coq10 in PCOS women. All the studies were with clomiphene citrate resistant PCOS women. They used clomiphene citrate for ovulation induction but we used letrozole. Letrozole is now recommended as first line for ovulation induction in PCOS.[1]

The first report of the potential reproductive effect of Coq10 in clomiphene citrate resistant PCOS women was a randomized controlled trial by El Refayee et al.[5] A total 101 infertile women with PCOS were randomly allocated into two groups: combined Coq10 and clomiphene citrate (51 patients, 82 cycles) and clomiphene citrate alone (50 patients, 71 cycles). Coq10 plus clomiphene citrate group received clomiphene citrate 150 mg/day from second to sixth day of cycle and Coq10 60 mg orally thrice daily from second day of cycle. The number of follicles >14 mm and ≥18 mm was significantly higher in the Coq10 group ($p<0.05$ and $p<0.001$ respectively). The endometrial thickness on the day of HCG administration was significantly greater in the Coq10 group (8.82±0.27 versus 7.03±0.74 mm, $p<0.001$). Ovulation occurred in 54/82 cycles (65.9% in Coq10 group) and 11/71 cycles (15.5%) in the control group which was significantly different ($p<0.001$). In the Coq10 group clinical pregnancy rate was 37.3% and in control group it was 6.0% and the difference in pregnancy rate was statistically significant ($p<0.001$).

The next relevant study was published by Lakshmi et al.[6] It was a prospective comparative interventional study on 40 PCOS women grouped into two: Coq10 and clomiphene citrate (20 patients) and clomiphene citrate only (20 patients). Coq10 plus clomiphene citrate group received clomiphene citrate 100 mg/day from second to sixth day of cycle and Coq10, 100 mg orally daily from second day of cycle. The number of follicles >14 mm was increased in the Coq10 plus clomiphene citrate group compared to clomiphene citrate only group (10.70±0.79 versus 5.65±0.58, $p<0.0001$). The number of 18 mm follicles were also increased in the Coq10 plus clomiphene citrate group compared to clomiphene citrate only group (12.25±0.70 versus 4.85±10.49, $p<0.0001$). The endometrial thickness was significantly less in the Coq10 plus clomiphene citrate group (3.15±0.4661 versus 5.55±0.5348, $p>0.02$). Ovulation occurred in 50% of the Coq10 group and 45% of the control group. Clinical pregnancy occurred 10% in control group and 5% in Coq10 group. The author explained the discrepancy in ovulation rate and clinical pregnancy rate by adverse effects of clomiphene citrate on the endometrium and cervical mucus.

Ibrahim did a prospective randomized controlled trial on infertile PCOS women resistant to clomiphene citrate.[7]

One group received clomiphene citrate 100 mg/day from day 3 to day 7 of the cycle and the other group in addition had 200 mg/day of Coq10. The ovulation rate was significantly higher in women having Coq10 (66.6% vs 18.3%). The cumulative pregnancy rate was also higher (47.8% vs 3%) and abortion rate lower (2.7% vs 6.7%). The study concluded that Coq10 was beneficial in increasing the rate of ovulation and clinical pregnancy rate and in decreasing early pregnancy loss in PCOS women.

The number of mature follicles (≥18-25 mm) was higher in women given Coq10 in all three cycles. This result corresponds with the results of El Refaeey et al and Lakshmi et al. The mean endometrial thickness was significantly higher in women having Coq10 in all three cycles. Similar results were found by El Refaeey et al but not by Lakshmi et al.[5,6] The reason may be the adverse effects of clomiphene citrate on the endometrium not found with letrozole.

In analyzing the ovulation rates of two groups, our study figured out that the ovulation rate was higher in the study group in all three cycles and significantly higher in second and third cycles. El Refaeey et al and Laksmi et al also found significantly higher ovulation rate in study group receiving Coq10.[5,6]

In the present study pregnancy rate was higher in study group in all three cycles. But statistically this result was not significant (p=0.177, p=0.167, p=0.258). El Refaeey et al and Lakshmi et al concluded that the increase in clinical pregnancy rate was statistically significant (p<0.01).[5,6] The higher p value may be explained by small sample size in our study as many participants were lost to follow up due to repeated lockdown in COVID 19 pandemic situations.

A prospective comparative study was done by Kuru Pekcan et al on 130 sub fertile PCOS women who had ovulation induction and intrauterine insemination after short term Coq10 supplementation or no supplementation.[8] Study group participants took Coq10 at a dose of 100mg daily for one month. The control group had no treatment. They stated that short term Coq10 supplementation was not effective as adjuvant for improving pregnancy rates in sub fertile women with PCOS. In our study as well as other studies the positive effects were more apparent beyond the first month of administration of Coq10.

Preclinical animal study by Bentov et al showed that Coq10 increased reproductive life time of female mice by about 30% and animals that received more Coq10, produced more and healthier eggs and showed improved ovarian response.[9] Yahya et al conducted study on clomiphene resistant PCOS women receiving Coq10 200 mg/day for two months in addition to clomiphene citrate 100 mg/day (for 5 days in each induction month).[10] There was post treatment decrease in serum free testosterone, LH, LH: FSH ratio and serum glutathione and a ovulation rate of 76.5%. Samimi et al conducted a double-blind, placebo-controlled trial on sixty PCOS women.[11] After 12 weeks of intervention with Coq10 there was a significant decrease in fasting plasma glucose (0.24±0.51 vs 0.01±0.44 mmol/l, p=0.04) and serum insulin concentration (p<0.001) in comparison to placebo.

Statistical significance testing is not enough to decide whether there is a clinically significant outcome.[12] So, we described the possible benefits of the new treatment with a binary or dichotomous variable such as the presence or absence of desired outcome (mature follicle, endometrial thickness ≥7 mm, ovulation and pregnancy). The effect sizes were reported and interpreted in terms of relative risks. Mature follicle, ovulation and pregnancy were more than 2 times likely to be achieved with addition of Coq10 to letrozole during ovulation induction in PCOS women.

Limitations

There were many limitations of the trial. Study population was recruited from only one selected tertiary center in Dhaka city thus limiting the external validity. It was a study of short duration with small sample size and substantial attrition. Serial transvaginal sonography was appropriate for determination of ovulation but was avoided to minimize exposure risk of COVID-19 infection. Data collection, follow up was challenging due to COVID-19 situation. Regarding the trial of bias, there was absence of blinding of participants and personnel dispensing the drugs and absence of blinding of outcome assessment. Outcome data was incomplete as there was drop out of participants in both arms.

CONCLUSION

The co-treatment with Coq10, an antioxidant during ovulation induction with letrozole is more effective than letrozole alone in infertile women with PCOS in terms of achieving mature follicle and favorable endometrial thickness more frequently, higher ovulation rates, and improved pregnancy rate. Randomized controlled trials may be designed with Coq10 as pre- treatment along with co-treatment during ovulation induction with letrozole. Further multi-center, large sample and long-term clinical trials are required to support current conclusions. Varied doses and duration of Coq10 treatment can be investigated to find out the optimum range for standard ovarian response.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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