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A study on quality of life and effect of coenzyme-Q10 in polycystic ovarian syndrome patients

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ABSTRACT

Background: Polycystic ovarian syndrome, commonly known as PCOs. It is the most common endocrine disorder in women involving cyst formation on ovaries which eventually affects the hormonal imbalance and is now well evidenced with obesity, insulin resistance, hyperandrogenism, abnormal lipid profile and oxidation stress.
Subjects and methods: This prospective comparative & interventional study evaluated QOL & effect of CoQ10 in PCOs patients.
Results: Out of 40 patients,30 are married and 10 are unmarried.8 are between 18-22years,13 are between 21-23 years,7 are between 24-26 years,7 are between 27-29 years,3 are between 30-32 years,2 are between 33-35 years.32 are having Irregular menses as major complaint & 8 are having An ovulation as major complaint.20 are between 1-2years of onset of disease,3 are between 2-3 years of onset of disease,7 are between 3-4 years of onset of disease and7 are between 4-5 years of onset of disease.13 are tested with PCOS between 18-22years,9 between 23-27 years,3 between 28-32years & 2 between 33 & above years.10 are suffering from PCOS between 18-22 years,5 are between 23-27 years,2 are between 28-32 years, 2 are between 33 & above years.8 women are aware of infertility due to PCOS between 18-22 years, 3 are between 23-27 years,5 are between 27-32 years,2 are between 33 & above years.
Conclusion: The present study revealed that majority of women was aware of PCOS. A few of them already tested themselves for PCOs.CoQ-10 was well tolerated by all the patients and no adverse effects were observed. The lack of any statistically significant differences in the ovulation and clinical pregnancy rates between lean and obese PCOS in the CoQ-10 group suggests that response to CoQ-10 group is independent of body weight, contrary to other methods of ovulation induction.

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INTRODUCTION

Polycystic Ovarian Syndrome, commonly known as PCOS (Scalzo and McKittrick, 2000). It is the most common endocrine disorder in women involving cyst formation on ovaries which eventually affects the hormonal imbalance in their body (Garad et al., 2011). It has significant reproductive and non-reproductive consequences (Franks. 1995). PCOS is mainly categorized into two types. They are Insulin-Resistant PCOS and Non-Insulin resistant PCOS. Insulin-resistant PCOS is also referred to as Type1 PCOS which include weight gain, facial hair, Ovulatory interruptions, hair loss, acne. Non-insulin resistance PCOS is referred to as Type 2 PCOS but don't represent with insulin resistance. The main cause of this type of disease is Iodine deficiency, Vitamin-D deficiency, hormone-disrupting toxins, thyroid disease and adrenal stress.

PCOS can be classified into tendency, mild form, moderate form, severe form based on the major and

minor criteria. Major criteria involve anovulation, oligomenorrhoea, hyperandrogenaemia, Severe hirsutism, insulin resistance and minor criteria involve ultrasound, elevated FSH: LH, obesity, hirsutism, and acne. It is now well evidenced that PCOS is associated with obesity, insulin resistance, hyperandrogenism, abnormal lipid profile and oxidation stress. Recently, PCOS was 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 (Imani et al., 1998). Although PCOS is an endocrine disease, it affects many systems of the body resulting in reproductive, metabolic, and psychological consequences (Hull et al., 1987).

PCOS means that the ovaries aren't getting the right (hormonal) signals from pituitary gland. Without these signals, women won't ovulate (make eggs) every month. The period may be irregular, or they may not have a period (Dahlgren et al., 1992). Oxidative stress one of the major causes of the polycystic ovarian syndrome. Oxidative stress is commonly referred as the imbalance between oxidants and antioxidants. When the imbalance favors oxidants, generation of excessive amounts of reactive oxygen species harm our body in various ways (Sabuncu et al., 2001) through the generation of excessive amounts of reactive oxygen species. Oxidative stress, which is generally known to be present in women with PCOS regardless of whether they are lean or have metabolic abnormalities, has been documented in infertile women. Unstable and highly reactive, free radicals achieve stability by stealing electrons from nucleic acids, proteins, lipids, carbohydrates, and other nearby molecules (Agarwal et al., 2005), thus inducing cellular damage.

The two major forms of free radicals are ROS & RNS. Free electrons typically form reactive oxygen species during oxygen reduction as a by-product of natural metabolic pathways (Agarwal et al., 2006). ROS are free radicals with oxygen centers. Several basic cellular processes lead to the production of ROS within a cell. Cellular respiration involves the reduction of molecular oxygen (O2) to water in the electron transport chain. RNS are free radicals with nitrogen centers. The two major examples are NO (Nitric oxide) & NO2 (Nitrogen dioxide). Under the normal physiological process, NO acts in a variety of tissues to regulate normal cell functions, but an excess of NO can be toxic (Agarwal et al., 2005).

Antioxidants stop the free radical chain reaction and donate one of their own electrons. Antioxidants during their electron donation don't become a free electron but allow the pairing of free radicals. Antioxidants are molecules which can safely interact with free radicals and terminate the chain reaction before vital molecules are damaged. They help our body to fight back and repair itself from inside out & give free radicals the electron they are looking for stabilizing them before they damage ourselves. Increased antioxidant levels decrease the free radical levels. Antioxidants scavenge excess ROS to counteract the potential for significant cell damage by excess ROS. Antioxidants help create a balance between beneficial oxidant generation (frequently act as cell signaling molecules) & damaging oxidative stress. There are two categories of antioxidants: enzymatic and non-enzymatic. Enzymatic antioxidants include SOD, catalase, and GPx. Non-enzymatic antioxidants include GSH, α-tocopherol (vitamin E), β-carotene, ascorbate (vitamin C), taurine, L-carnitine, coenzyme Q10, here are three SOD isoforms in eukaryotes: manganese SOD (Mn-SOD), copper/zinc SOD (Cu/Zn-SOD), and extracellular SOD (EC-SOD) (Norman et al., 2007).

Antioxidant supplementation CoQ10 can neutralize free radicals and may reduce or even help prevent some of the damage caused. As an energy carrier, the Coq10 molecule continuously goes through an oxidation-reduction cycle. As it accepts electrons, it becomes reduced. As it gives up electrons, it becomes oxidized. In its reduced form, the CoQ10 molecule holds electrons rather loosely, so this CoQ10 molecule will give up one or both electrons quite easily and thus act as an antioxidant (Sies, 1985). CoQ10 is a mitochondrial antioxidant, a substance that protects the mitochondria from damage caused by either insulin resistance or oxidative stress caused by free radicals. It had a significant increase in the numbers of healthy egg follicle. Endometrial lining thickness was also significantly increased.

SUBJECTS AND METHODS

The study comprised of 40 women among those attending the tertiary patient care, in the period from December 2016 to August 2017. Diagnosis of PCOS based on the revised 2003 consensus on diagnostic criteria and long-term health risks related to PCOS (The Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group, 2004). All women were previously given the PCOSQ and an Informed Consent form. The exclusion criteria of this study included patients with psychologically ill patients, Patient who is not willing to participate in the study, Patient suffering from Diabetes, Pregnant women, Women on Breastfeeding.

The study was approved by the departmental ethical committee and all participants gave informed consent before inclusion in the trial. A questionnaire was prepared to study the awareness of PCOS among

women of different age groups which contains a total of 21 questions. The study was conducted o 40 patients who were selected from tertiary care hospitals. The questionnaire was printed n the format of yes or no questions and was supplied to the patients. After the data collection, statistical measurements were done using Microsoft Excel.

PCOs QUESTIONNAIRE			
Name:		**Age:**	**W/o/D/o:**
BP:		**Weight:**	**Contact:**
YES	NO	1. Do you crave for carbohydrates and sugar?	
YES	NO	2. Do you have continuous weight gain?	
YES	NO	3. Do you have difficulty with losing weight?	
YES	NO	4. IS your waistline greater than 35 inches?	
YES	NO	5. Did you had problems in the past with acne?	
YES	NO	6. Do your cycle last longer than 35 days?	
YES	NO	7. Does periods are unpredictable.	
YES	NO	8. My periods last longer than a week.	
YES	NO	9. My periods are very heavy or prolonged.	
YES	NO	10. Do you have excess facial hair.	
YES	NO	11. Do you have symptoms of hypoglycemia.	
YES	NO	12. Does your family have a history of diabetes.	
YES	NO	13. Does your family have a history of cardiovascular disease.	
YES	NO	14. Do you have a history of gestational diabetes	
YES	NO	15. Did you notice pigmentation changes.	
YES	NO	16. Do you have a history of high blood pressure.	
YES	NO	17. Do you have had difficulties getting pregnant.	
YES	NO	18. Do you have unusual amount of hair on breasts.	
YES	NO	19. Do you have hair growth on upper thighs.	
YES	NO	20. Do you have pubic hair that grows up abdomen and around the navel.	
YES	NO	21. Is your acne worse at different times of cycle.	

Patients were grouped into two: CoQ10 & clomiphene citrate (20 patients enrolled) and clomiphene citrate only (20 patients enrolled). Allocation process was done by an Investigator. CoQ10/clomiphene citrate patients received clomiphene citrate (Clomid/ Fertomid, Svizera, Cipla) 100mg/day from cycle days 2–6 for 45 days and CoQ10 (Co-enzyme Q10, Tirupati Life Sciences), in a dose of 100 mg capsules orally once a day starting on cycle day 2 for 45 days. Choice of dose and duration of administration of CoQ10 has chosen arbitrarily because of the lack of previous human experience. Patients in the control group received clomiphene citrate 100 mg/day from cycle day 2 for 45 days. No patients received ovulatory medications in the 3 months previous to the study were chosen for the CoQ10 group. All participants were instructed not to take any medications during the trial except after consultation with the physician.

All patients were monitored by transvaginal ultrasound for follicular diameter and endometrial thickness on cycle days 10, 12 and 14. The physicians monitoring the cycles were not blinded to the protocol of each group.

The primary outcome measures were the number of growing and mature follicles, serum oestradiol, FSH; LH, ovulation rate and endometrial thickness. Secondary outcome measures were the occurrence of clinical pregnancy.

Statistical analysis

Before starting the study, sample size calculation was done. Twenty cases were needed in each arm to gain a significant difference of 22% in pregnancy rate at a significant level of 5% and a study power of 80%. Data obtained were statistically analyzed using the Graph pad prism.7.0 Software. The mean and standard deviation was analyzed by Student′s t-test. Differences were considered significant when $P < 0.0001$.

RESULTS

The study on PCOS awareness was done and analysis of the data was carried out based on the age groups. It was seen that amongst 40 participants, 25% of women were found to be suffering from PCOS. The percentage awareness about PCOS as well as female infertility, the percentage of women who have tested themselves for

PCOS and opinion of women regarding the inclusion of PCOS is shown in figure no 1.

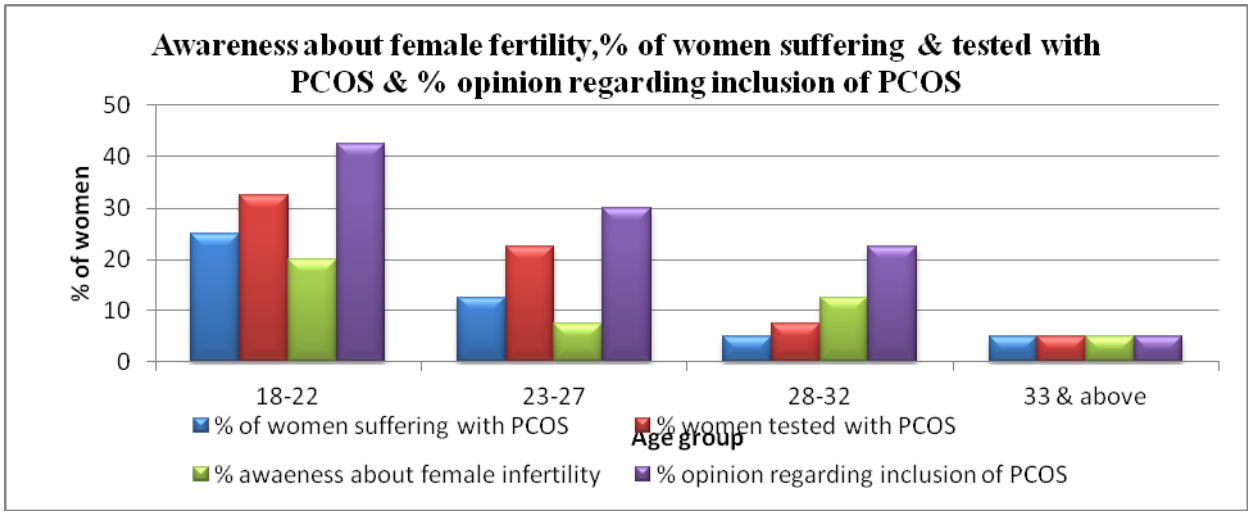

Figure 1. Patients awareness on PCOs based on age group.

The awareness about the Diagnostic tests available for PCOS was also collected for few well known and majorly used Diagnostic tests. The percentage of women aware about various test and women having no knowledge about these tests are described below in the figure 2.

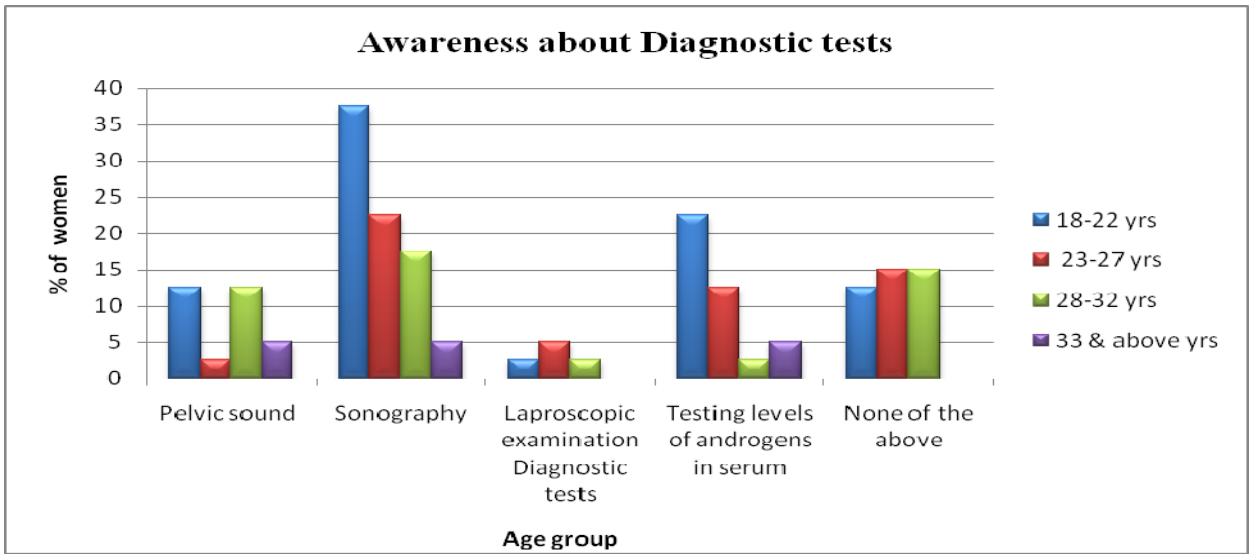

Figure 2. Awareness about the diagnostic tests.

Table 1. Percentage response of participants towards the awareness of symptoms and treatments available.

Age group		18-22	23-27	28-32	33 & above
Total		17	12	9	2
Symptoms		%	%	%	%
1	Menstural irregularities	88.2	75	87.5	100
2	Anovulation	47	25	55	-
3	Facial & Abdominal hair growth	64.7	90	87.5	50
4	Weight gain	65.7	66.5	75	50
5	Pigmentation changes	41.1	74.6	25	100
6	Acne	88.2	58.3	62.5	100
7	Abdominal pain	94.1	75	85	100
Treatments		%	%	%	%
1	Oral contraceptives	23.5	50	55.5	100
2	Clomiphene citrate	17	16	11.1	0
3	Weight loss & diet adjustment	29.4	41.6	11.1	0

The study comprised of 40 patients in total. There were no statistical significant differences between the two groups with regard to age, parity, duration of infertility, body mass index, the presenting symptoms and signs and hormonal profile (Table 2).

Table 2. Patient characteristics.

Patient Characteristics	COQ-10 n=(20)	Clomiphene citrate n=(20)
Age	24.05±0.87	24.7±1.14
Parity	0.4±0.31	0.3±0.33
Clinical Presentation		
Oligo/Anovualtion	8(40)	7(35)
Polycystic ovaries	19(95)	17(85)
Hyperandrogenism	16(80)	15(75)
Duration of infertility (yrs)	2.50±1.511	2.37±1.685
Irregular menses	19(95)	17(85)
BMI	33.22±2.209	29.97 ± 1.207
LH	11.49±2.900	11.44±2.593
FSH	9.64±2.693	9.23±2.196
T3	0.61±0.661	1.18±1.319
T4	3.82±3.902	5.26±3.885
TSH	3.44±2.577	3.70±2.655

Values are mean ± SD or n (%). There were no statistically significant differences between the groups.

BMI = body mass index.

The number of follicles >14 mm and 18 mm were significantly increased in the CoQ10 group (P <0.0001) respectively (Table 3). The endometrial thickness was significantly lesser in the CoQ10 group (5.55±0.5548mm versus 3.15±0.4661mm).

Table 3. Patients response after treatment with clomiphene citrate & CoQ10.

	Clomiphene citrate (n=20)	CoQ10 (n=20)	P-Value
No. of follicles>14mm	5.65± 0.58	10.70± 0.79	P<0.0001
No. of follicles>18mm	4.85± 10.49	12.25± 0.70	P<0.0001
Endometrial thickness (mm)	5.55± 0.5548	3.15± 0.4661	P>0.02
Serum oestradiol	4.15± 0.5345	15.25± 1.015	P<0.0001
Clinical pregnancy per patient	1(5)	2(10)	P<0.001

Values are mean ± SD or n (%).

The number of follicles >14 mm and >18 mm were significantly higher in the CoQ10 group (P<0.0001 and P < 0.001 respectively; Table 3). The endometrial thickness administration was significantly greater in the CoQ10 group (5.55 ± 0.55 mm versus 3.15 ± 0.46 mm, P >0.02). Ovulation occurred in 9 (45%) in the CoQ10 group and 10 (50%) in the control group, which was significantly different (P < 0.001). Serum oestradiol significantly higher in the CoQ10 group (P < 0.0001). In the CoQ10 group, clinical pregnancy occurred in 2/20 women (10%), and in the control group, clinical pregnancy occurred in 1/20 women (5.0%), (P < 0.001) (Table 3).

Table 4. Treatment outcomes in lean and obese PCOs patients treated with Clomiphene citrate.

	Lean PCOs (n=8)	Obese PCOs (n=12)	P-Value
No. of follicles>14mm	5.67± 0.84	5.63± 0.80	P</= 0.0001
No. of follicles>18mm	3.77± 0.54	6.50± 0.42	P<0.0001
Endometrial thickness(mm)	5.11± 2.472	7.07± 2.483	P<0.0001
Serum oestradiol	2.72± 1.332	3.83± 2.227	P<0.0001
Clinical pregnancy per patient	1(11.1)	0(0)	p>0.001

In the CoQ10 group, 8 women with lean PCOS, the ovulation rate was 62.5% and the clinical pregnancy rate was 12.5%. Of 12 women with obese PCOS, the ovulation rate was 33.3% and the clinical pregnancy rate was 8.3%. Endometrial thickness was significantly increased (P < 0.0001) in women with obese PCOS versus lean PCOS. There was significant differences (i.e increased) regarding number of follicles and serum oestradiol (Table 5). When the control group was stratified into lean (9 women)whose ovulation rate was 77.7% and in obese (11 women),ovulation rate was 36.36%, no statistically significant differences were found in number of follicles>14mm, serum oestradiol was found to be increased in Obese patients, clinical pregnancy rates (11.1%versus0%)were found to be equal in both lean & obese Patients (Table 5).

DISCUSSION

We have demonstrated from this study that out of 40 participants, 62.5% of them were aware of PCOS. Awareness about PCOS was highest among the age group of 18-22 years. Similar research has been done under different conditions by E. Scott et. al., 2001 and they have reported that there is a significant increase regarding awareness of PCOS among women. PCOS is a common cause of an anovulation and female infertility.

The infertility rate with the polycystic ovarian syndrome is high; these women will have difficulty in getting pregnant and usually require treatments to improve chances of pregnancy.

Table 5. Treatment outcomes in lean and obese PCOS patients treated with CoQ10.

	Lean PCOs (n=9)	Obese PCOs (n=11)	P-Value
No. of follicles>14mm	12.45± 0.67	8.56± 1.24	P>0.0001
No. of follicles>18mm	9.56±0.38	13.3± 0.76	P<0.0001
Endometrial thickness (mm)	6.87± 1.667	6.93± 2.068	p<0.0001
Serum oestradiol	16.05± 3.560	15.51± 5.142	p>0.0001
Clinical pregnancy per patient	1(12.5)	1(8.3)	p</= 0.0001

This study also shows that very less number of women are aware of the treatments which are available for PCOS. From, this study it was observed that only 40% of women are aware of the fact that long-term PCOS condition can lead to infertility. This study has shown that about 85% of women are suffering from menstrual irregularities in PCOS women, and 40% are showing anovulation.

Oxidative stress is a term that was introduced by Sies, in 1985 occurs due to an imbalance between the production of ROS, called the oxidative load, and the antioxidant defense system (Agarwal et al., 2008). The oxidative load is described as "a measure of the steady-state level of reactive oxygen or oxygen radicals in a biological system". Disturbances in the normal redox state of cells can cause toxic effects through the production of peroxides and free radicals that damage all components of the cell, including proteins, lipids, and DNA . The mononuclear cells of women with PCOS are increased in this inflammatory state (Gonzalez et al., 2006), which occurs more so from a heightened response to hyperglycemia and C-reactive protein (CRP). Physiological hyperglycemia generates increased levels of ROS from mononuclear cells, which then activate the release of TNF-alpha and increase inflammatory transcription factor NF-kappa B. As a result, concentrations of TNF-alpha, a known mediator of insulin resistance, are further increased. The resultant OS creates an inflammatory environment that further increases insulin resistance and contributes to hyperandrogenism (Costello et al., 2007). Oxidative stress from oxidative metabolism causes base damage by forming ROS AND RNS and strand breaks in DNA. Base damage is mostly indirect and caused by reactive oxygen species (ROS) generated, e.g. O2– (superoxide radical), OH (hydroxyl radical) and H2O2 (hydrogen peroxide) (Chandra Kala et al., 2015). In women, Oxidative stress might play a role in infertility. The Haber-Weiss reaction, given below, is the major mechanism by which the highly reactive hydroxyl radical (OH*) is generated (Liochev et al., 1999), which can generate more toxic radicals through interaction with Superoxide (SO) & Hydrogen peroxide (H2O2).

$$O2+- +H202>O2+OH-+OH^{*}$$

Most ROS are produced when electrons leak from the mitochondrial respiratory chain, also referred to as the electron transport chain (ETC) (Fujii et al., 2005). Mitochondria are essential for the ATP production which is energy responsible for the gametic functions. Mitochondria produce ROS. However, excessive ROS can affect functions of the mitochondria in oocytes and embryos (e.g., damage to DNA, lipid membranes, and proteins). This mitochondrial dysfunction may lead to the arrest of cell division, triggered by OS (Liu et al., 2000; Liu et al., 2000).

OS is involved in the pathological processes of IR, hyperandrogenemia, and obesity as well, which accompany PCOS frequently but not absolutely (Zuo tao et al., 2006).Thus, appropriate markers should be chosen to evaluate the OS levels in PCOS for the particular circumstance. Current employed circulating markers majorly include homocysteine, malondialdehyde (MDA), asymmetric dimethylarginine (AMDA), superoxide dismutase (SOD), glutathione (GSH), and paraoxonase-1

(PON-1)Obesity is one of the important factors contributing to the increased OS levels in PCOS but not the only one.

Recently, a study examining murine oocytes concluded that the poor oocyte quality of insulin-resistant mice was a result of oxidative damage to mitochondrial functions. The mitochondrial dysfunction in PCOS patients (Hardiman et al., 2003; Victor et al., 2011) occurs secondary to decreased consumption (OuXH et al., 2012) of O2 and increased generation of ROS, with a decline in antioxidant levels (Gonzalez et al., 2006; Palacio et al., 2006).

As far as is known, this is the first report of the potential reproductive effects of CoQ10 in human females performed only for 45 days. Animal studies have reported that CoQ10 increases the reproductive lifetime of female mice by about 30% and that animals that receive more CoQ10 produce more and healthier eggs and show improved ovarian response and various consistent hormonal changes (Bentov et al., 2010).

In this study of 40 patients in total, there was no statistical difference between the two groups with

regard to age, parity, duration, and infertility, BMI, the presenting symptom and signs and hormonal profile (Table 2).

The results demonstrate that therapy with CoQ10 significantly improves clinical pregnancy rates in clomiphene-citrate-resistant PCOS women. The discrepancy between ovulation rate and clinical pregnancy rate among CoQ10-clomiphene citrate-treated women may be due to adverse effects of clomiphene citrate on the endometrium as well as on the cervical mucus. The improved clinical pregnancy rate in the CoQ10 group compared with the control group is probably related to improved ovarian response in the CoQ10 group, higher oestradiol concentration in the CoQ10 group shows better ovulatory response & the number of follicles >14 mm and >18 mm were significantly higher in the CoQ10 group ($P < 0.0001$ and $P < 0.0001$ respectively).

CoQ10 was well tolerated by all the patients and no adverse effects were observed. The lack of any statistically significant differences in the ovulation and clinical pregnancy rates between lean and obese PCOS in the CoQ10 group suggests that response to CoQ10 is independent of body weight, contrary to other methods of ovulation induction such as gonadotrophins. However, further studies with a large number of patients are recommended to verify these findings. To avoid bias, patients in the control group were informed not to take any medication unless with the permission of the treating physician while receiving clomiphene citrate, particularly CoQ10, as well as not to take medications known to affect CoQ10 such as beta-blockers and tri-cyclic antidepressants.

The results of this study are encouraging; however, the appropriate dosage of CoQ10 and the optimal duration of treatment need to be further investigated. Comparing CoQ10 with other medical methods of ovulation induction in cases of clomiphene-citrate-resistant PCOs, CoQ10 is not as time-consuming as metformin, which requires 1–6 months, and it is not as expensive as gonadotrophins and does not need intensive monitoring during and after treatment.

CONCLUSIONS

In conclusion, the study revealed that majority of the women was aware of PCOS. A few of them already tested themselves for PCOS. Quite a considerable number of women in the age group of 18-22years are aware of the availability of treatment for the same. A high percentage of women had agreed to the idea of including PCOS as a part of educational intervention programme would be beneficial to avoid complications.

CoQ10 seems to be a promising Antioxidant to oral ovulatory agents such as clomiphene citrate. C0Q10 is proved to be effective, inexpensive and safe for stimulating follicular development and can be tried successfully before a more complicated treatment such as gonadotrophins and laparoscopic ovarian drilling.

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CONFLICTS OF INTEREST

None declared.

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