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Effect of Ubiquinol supplementation on ovulation induction in Clomiphene Citrate resistance

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Abstract

Background: Clomiphene Citrate is considered the gold-standard for induction of ovulation and has been used for several years to treat PCOS related infertility. Unfortunately, 15-40% of women with PCOS are resistant to Clomiphene Citrate. The study aimed to evaluate potential benefits of adding the active form of Coenzyme Q10 (Ubiquinol) to Clomiphene Citrate compared with Human Menopausal Gonadotropins (hMG) in Clomiphene Citrate resistant PCOS patients. 148 PCOS Patients with Clomiphene Citrate resistance were randomized into two groups (A and B). In group A, controlled ovarian stimulation was done by Clomiphene Citrate 150 mg daily (from 2nd till 6th day of cycle) together with Ubiquinol starting from 2nd day till day of hCG triggering in a dose of 100 mg orally once daily. In group B, hMG was given from 2nd day of the cycle in a dose ranging from 75 to 225 IU. Serial transvaginal ultrasonography was done starting on cycle day 8 and continued till size of leading follicle reaches 18 mm or more then ovulation triggering was done. Thereafter, patients were advised for a timed intercourse (TI) after 36 hours. A blood sample was withdrawn seven days after hCG triggering, for measurement of serum progesterone. If the Patient presented with a missed period for one week, a serum sample was sent for β-hCG.

Results: There were no statistically significant differences ($P > 0.05$) between studied groups regarding; number of cases reaching mature follicular size, number of stimulated cycles, endometrial thickness on the day of hCG triggering, mid-luteal serum progesterone, positive serum pregnancy test and clinical pregnancy rate.

Conclusions: Addition of Ubiquinol to Clomiphene Citrate improved ovarian responsiveness in Clomiphene Citrate resistant patients with results comparable to conventional hMG stimulation protocol.

Keywords: Clomiphene Citrate resistance, Ubiquinol, Coenzyme Q10, PCOS

Background

Seven to eight percent of women in reproductive age have polycystic ovary syndrome (PCOS) which is characterized by hyperandrogenemia and chronic anovulation [1]. Proper management of PCOS is based on accurate diagnosis. Rotterdam criteria have been widely used for diagnosis of PCOS, it requires two of three features; ultrasound picture of polycystic ovary, ovulatory disorders and/or clinical/biochemical signs of hyperandrogenism [2].

Clomiphene Citrate (CC) is cheap, effective and safe drug; thus, it is the first line for induction of ovulation [3, 4]. About 15–40% of women with PCOS have Clomiphene Citrate resistance (CCR) which was defined as failure of ovulation after receiving 150 mg Clomiphene Citrate per day [4]. Many factors have been incriminated in Clomiphene Citrate resistance including androgen excess, insulin resistance (IR), increased body mass index (BMI) [5] and hereditary predisposition [6].

Many dietary supplementations have a role in health promotion and had abundant attention in the last few years. Coenzyme Q10 (CoQ10) is a benzoquinone which is lipid-soluble and is being involved in the respiratory

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chain of mitochondria for ATP production [7]. CoQ10 is a good antioxidant because it has the ability to maintain continuous cycles of oxidation-reduction [8]. Many recent studies concluded that CoQ10 supplementation improves endocrine and metabolic functions of PCOS patients [9, 10]. Also, it improves insulin resistance [11], causes reduction of blood pressure [12] and recovers endothelial functions [13].

The second-line therapy for induction of ovulation, in PCOS patients with Clomiphene Citrate resistance, is gonadotropins. Although, they have many disadvantages; being expensive, requiring meticulous follow up of patients during induction as there is high risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies [3, 14].

Aim of the study:

This study was conducted to evaluate the potential benefit of adding the active form of Coenzyme Q10 (Ubiquinol) to Clomiphene Citrate when compared with Human Menopausal Gonadotropins (hMG) in Clomiphene Citrate resistant PCOS patients, and eventually; the possibility of using Ubiquinol / Clomiphene Citrate combination as an alternative to the conventional hMG stimulation protocol.

Methods

The study was conducted in the department of Obstetrics and Gynaecology of the Saudi German Hospital, Madinah- Kingdom of Saudi Arabia, as a randomized clinical trial during the period from April 2019 to July 2020. The study protocol was approved by the local ethics committee. Before participating in the study, a written informed consent was obtained from all patients. The study included 148 patients with Clomiphene Citrate resistant PCOS who fulfilled the following inclusion criteria: age 18 to 35 years, Body mass index (BMI) between 18.5 and 34.9 kg/m2, presenting with primary or secondary infertility. PCOS was diagnosed according to the Rotterdam ESHRE/ASRM Consensus workshop [3], with at least 2 of the following 3 criteria:

A- Oligo- and/or anovulation; manifested by oligomenorrhea or amenorrhea. Oligomenorrhea was defined as cycle interval of more than 35 days but less than six months. Amenorrhea was defined as absence of menstruation for six months or more.

B- Hyperandrogenism; biochemical and/or clinical in the form of acne or hirsutism defined as a score of 8 or higher using the modified Ferriman–Gallwey scoring system [15] when abnormal hair distribution was assessed in nine body areas and given a score of 0 to 4.

C - Polycystic ovarian morphology detected by transvaginal ultrasound with the presence of 12 or more follicles measuring 2–9 mm in diameter in one or both ovaries, and/or increased ovarian volume >10 mL.

With exclusion of other etiologies that may also lead to oligoovulation and/or androgen excess such as androgen-secreting tumors, congenital adrenal hyperplasia, hyperprolactinemia or Cushing's syndrome.

Patients with anovulation who had clinical or laboratory evidence for hyperandrogenaemia were primarily assessed for the cause before establishing the diagnosis of PCOS and indeed before exposure to clomiphene citrate as a first line for ovulation induction. In this study, we enrolled only PCOS patients with clomiphene citrate resistance. Patients with hyperandrogenaemia due to other causes such as, androgen secreting tumours diagnosed when the level of testosterone is higher than 2 ng/mL, and congenital adrenal hyperplasia diagnosed by high level of 17-OH progesterone, were excluded.

Clomiphene Citrate resistance was defined as failure of ovulation after administration of Clomiphene Citrate in a dose of 150 mg for 5 days per cycle, for two or three cycles [4]. All Patients had patent both fallopian tubes and normal uterine cavity as evidenced by hysterosalpingography (HSG) and their partners had normal semen parameters as defined by the modified WHO 2010 criteria [16].

Exclusion criteria were: Morbidly obese patients with BMI ≥35 Kg/2m, abnormal husband semen analysis, abnormal HSG or laparoscopic evidence of pelvic adhesions. Patients receiving statin drugs for cholesterol, beta-blockers for high blood pressure, or tricyclic antidepressants, were also excluded as these drugs can lower the levels of ubiquinol in the body.

Initial Assessment

All patients were initially assessed at the booking visit, with detailed history taking, including personal, medical, surgical, obstetric and menstrual history. The body mass index (BMI) was calculated. Basal hormonal profile; serum follicle stimulating hormone (FSH) and luteinizing hormone (LH), were measured using Enzyme Linked Immunosorbent Assay (ELISA).

Ovarian stimulation and folliculometry

Patients were divided randomly into two groups (A and B), who underwent controlled ovarian stimulation and timed intercourse, using random table computer software (Open Epi version 3.21).

Basal transvaginal ultrasonography (TVS) was done on day 2 of the cycle before commencing ovarian stimulation. For patients presenting with amenorrhea or oligomenorrhea, dydrogesterone 10 mg (Duphaston®; Abbott Biologicals B.V.) was prescribed (3 times daily for 10 days) to achieve withdrawal bleeding before starting induction of ovulation.

In group A, controlled ovarian stimulation (COS) was done by Clomiphene Citrate (Fertab® 50 mg tablets,

Zynova. SITCO Pharma.) as 150 mg (3 tablets) daily for 5 days (from 2nd day till 6th day of the cycle) together with Ubiquinol (active form of Coenzyme Q10) starting from 2nd day till the day of human Chorionic Gonadotropin (hCG) triggering in a dose of 100 mg capsules orally once daily, immediately after meal (Nutraquinol®; Jamjoom Pharma Nutraceuticals). In group B, Human Menopausal Gonadotropins (hMG) (Merional® 75 I.U. vials, IBSA.) IM was given from 2nd day of the cycle in a dose ranging from 75 to 225 IU according to the patient's response. Patients were instructed not to take any non-study drugs during the whole study period. All patients did not receive any drug for induction of ovulation 3 months prior to participation in the study.

Patients were counselled regarding the possible side effects of Clomiphene Citrate such as: reversible enlargement of the ovaries, multiple pregnancy, ovarian hyperstimulation syndrome, blurred vision, light sensitivity, headache, hot flushes, mild abdominal pain and vaginal bleeding [17] as well as the possible side effects of Human Menopausal Gonadotropins such as: pain at the site of injection, abdominal discomfort and pelvic pain, breast discomfort, ovarian hyperstimulation syndrome, multiple pregnancy, weight gain, headache, mood changes, nausea, abnormal uterine bleeding, dizziness, ovarian cysts, adnexal torsion or ruptured ovarian cyst and ectopic pregnancy [18].

Serial transvaginal ultrasonography was done for assessment of follicular growth (number and diameter of follicles) and endometrial thickness (measured on sagittal view of the uterus by including the whole endometrium at the point of its maximum thickness), starting on cycle day 8, using vaginal 4.5 MHz endocavity transducer (Esaote Mylab 50 Xvision Ultrasound, Italy), and was continued with an interval of 1-3 days till the size of the leading follicle reaches 18 mm or more in mean follicular diameter. Then ovulation triggering was done by an intramuscular single dose of human Chorionic Gonadotropin (Epifasi® 5000 IU vials, EIPICO, Egypt.) 2 vials (10,000 IU). Thereafter, patients were advised for a timed intercourse (TI) 36 hours after ovulation triggering.

All measurements were obtained by a blinded single operator. All data were digitally stored and were not analyzed till the end of the study.

Thereafter, patients were asked to come for follow up, 7 days after hCG triggering, where a blood sample (2 mL) was withdrawn for measurement of serum progesterone (ng/ml). Collected samples were centrifuged and then stored at 2–8 °C until enzyme immunoassay was done. If the Patient presented with a missed period for a week, a serum sample was sent for β-hCG using immunoassay.

Patients with positive serum pregnancy test, defined as β-hCG concentration >10 mU/ml, were examined by abdominal ultrasonography 6 weeks after the first day of their last menstrual period with 3.5 MHz sector transducer (Esaote Mylab 50 Xvision Ultrasound, Italy) to detect an intrauterine gestational sac (Clinical pregnancy) [19]. Patients who failed to get pregnant were requested for follow up for 2 more consecutive cycles with the same protocol.

The primary outcomes measured were; number of cases achieving follicular growth to the size of mature follicle ≥ 18 mm (1–3 follicles) during the three cycles of stimulation, number of stimulated cycles (till pregnancy occurs or completing the 3 cycles of the study, whichever is earlier), the endometrial thickness on the day of triggering, and the luteal function as assessed by mid-luteal serum progesterone measurements.

The secondary outcomes were; number of cases with positive serum pregnancy test and the clinical pregnancy rate among the two groups during the three cycles of treatment.

2.3. Sample size calculation: was done using a computer software G Power® version 3.1.5 (Franz Faul, Universität Kiel, Germany).

Results

211 patients with Clomiphene Citrate resistant PCOS, presenting with primary or secondary infertility, visited the outpatient clinic during the study period. Assessment for eligibility was done and 175 patients were fitting the inclusion criteria. The protocol of study, the intervention involved, possible short- and long-term side effects of interventions were fully discussed with the patients. 161 patients were willing to participate and signed an informed consent for participation. Simple randomization of those patients was done where 81 cases were allocated in group A (ovarian stimulation by Clomiphene Citrate 150 mg daily for 5 days, from 2nd to 6th day of the cycle, together with Ubiquinol starting from 2nd day till the day of human Chorionic Gonadotropin (hCG) triggering in a dose of 100 mg capsules orally once daily), and 80 cases in group B (ovarian stimulation by Human Menopausal Gonadotropins (hMG) 75 to 225 IU IM from 2nd day of the cycle).

Patients who were dropped from follow up were excluded from the study statistics and results (6 and 7 patients from group A and B respectively). So, eventually, analysis was done for 148 patients (75 and 73 patients from group A and B respectively). The flowchart of the participants is shown in (Fig. 1).

Regarding the demographic and clinical parameters (i.e. age, BMI, type of infertility and duration of infertility), there were no statistically significant differences ($P > 0.05$) between the 2 studied groups as shown in (Table 1).

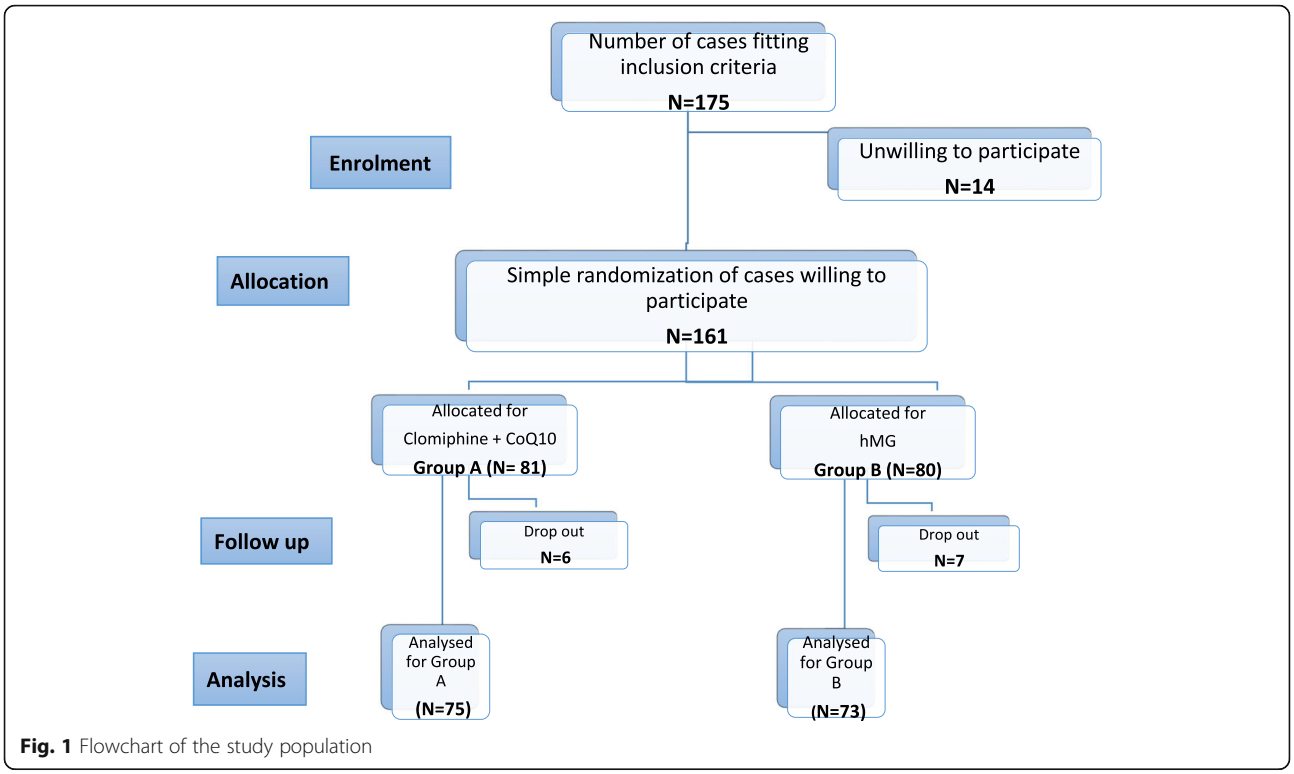

Fig. 1 Flowchart of the study population

Table 1 Demographic and clinical data of the study population

	All patients (N=148)	Group A (N=75)	Group B (N=73)	p-value
Age (years)				
Mean ± SD	26.59 ± 7.00	26.68 ± 6.99	26.51 ± 7.02	
≤20 years	23 (15.6%)	12 (16.0%)	11 (15.1%)	0.93
21 – 29 years	89 (60.1%)	44 (58.7%)	45 (61.6%)	
≥ 30 years	36 (24.3%)	19 (25.3%)	17 (23.3%)	0.92
BMI (kg/m^2)				
Mean ± SD	27.48 ± 4.80	27.34 ± 4.89	27.62 ± 4.71	
Average	34 (23.0%)	18 (24.0%)	16 (22.0%)	0.74
Overweight	83 (56.1%)	41 (54.7%)	42 (57.5%)	
Obese	31 (20.9%)	16 (21.3%)	15 (20.5%)	0.93
Type of infertility				
Primary	87 (58.8%)	44 (58.7%)	43 (58.9%)	
Secondary	61 (41.2%)	31 (41.3%)	30 (41.1%)	0.97
Duration of infertility (years)				
Mean ± SD	2.53 ± 1.48	2.47 ± 1.39	2.59 ± 1.57	0.63
FSH (IU/L)				
Mean ± SD	5.47 ± 2.25	5.67 ± 2.36	5.28 ± 2.15	0.31
LH (IU/L)				
Mean ± SD	5.24 ± 1.69	5.43 ± 1.74	5.05 ± 1.65	0.17
Testosterone (ng/mL)	0.64 ± 0.18	0.62 ± 0.15	0.66 ± 0.17	0.91

As regard the basal hormonal profile (serum FSH, LH and testosterone), there was no statistically significant difference (P > 0.05) between the 2 studied groups. The mean value for basal serum FSH levels in group A was 5.67 ± 2.36 IU/L compared to 5.28 ± 2.15 IU/L in group B. The mean value for basal serum LH levels for group A was 5.43 ± 1.74 IU/L compared to 5.05 ± 1.65 IU/L for group B. The mean value for serum testosterone levels for group A was 0.62 ± 0.15 ng/mL compared to 0.66 ± 0.17 ng/mL for group B (Table 1).

There were no statistically significant differences (P > 0.05) between the 2 studied groups regarding the number of cases reaching mature follicular size during the study period (60.0% compared to 64.4% in the first cycle, 59.2% compared to 63.2% in the second cycle, and 62.3% compared to 66.1% in the third cycle) as shown in (Table 2 & Fig. 2). Regarding the number of mature follicles (≥18 mm in diameter on the day of triggering) and the diameter of dominant follicles, there were no statistically significant differences between the 2 groups (P > 0.05) as shown in Table 2.

As regard the number of stimulated cycles during the study period, there were no statistically significant differences (P > 0.05) between the 2 studied groups (75 compared to 73 in the first cycle, 71 compared to 68 in the second cycle, and 61 compared to 59 in the third cycle) (Table 2 & Fig. 3).

Regarding the endometrial thickness on the day of hCG triggering, there was no statistically significant difference (P= 0.64) between both groups (8.98 ± 2.97 mm in group A compared to 9.21 ± 2.58 mm in group B) as shown in (Table 2).

As regard the mean values of mid-luteal serum progesterone, there was no statistically significant difference (P= 0.88) between both groups (10.73 ± 4.42 ng/mL in group A compared to 10.82 ± 4.57 ng/mL in group B) as shown in (Table 2).

Regarding the number of pregnancies diagnosed by positive serum pregnancy test, there was no statistically significant difference (P= 0.61) between both groups, with 15 pregnancies achieved in group A (20.0%)) compared to 17 pregnancies (23.3%) in group B (Table 3 & Fig. 4).

There was no statistically significant difference between both groups as regard the clinical pregnancy rate (P= 0.77) with 14 pregnancies (18.7%) achieved in group A compared to 15 pregnancies (20.5%) in group B (Table 3 & Fig. 5). As regard the number of cases of multiple pregnancy and the number of miscarriages, there were no statistically significant differences between the 2 groups (P= 0.38 and 0.69 respectively) as shown in Table 3.

Discussion

Ovarian function could be improved by CoQ10 supplementation through several mechanisms; it has antioxidant and anti-apoptotic activities, it also causes stabilization of cell membrane and improves mitochondrial ATP production [20]. Mitochondrial production of energy was significantly improved by CoQ10 supplementation [21]. Normal maturation, fertilization of oocyte, development of embryos and synthesis of steroid hormones could not be achieved except with good mitochondrial production of energy [22]. Oocyte mitochondrial dysfunction in the form of reduced mitochondrial adenosine triphosphate (ATP) production due to diminished oxidative phosphorylation will lead to reduced reproductive functions; decreased quality of oocyte, ovarian reserve, fertilization, and development of embryos [23, 24].

Table 2 The primary outcomes

Outcomes	All patients (N=148)	Group A (N=75)	Group B (N=73)	p-value
Cases reaching mature follicular size during the study period:				
Cycle 1	92 (62.2%)	45 (60.0%)	47 (64.4%)	0.712
Cycle 2	85 (61.2%)	42 (59.2%)	43 (63.2%)	0.711
Cycle 3	77 (64.2%)	38 (62.3%)	39 (66.1%)	0.722
Number of stimulated cycles during the study period *				
Cycle 1	148	75 (100%)	73 (100%)	1.00
Cycle 2	139	71 (94.7%)	68 (93.2%)	0.91
Cycle 3	120	61 (81.3%)	59 (80.8%)	0.96
Number of follicles ≥ 18 mm in diameter on the day of hCG triggering	1.19 ± 0.38	1.14 ± 0.34	1.24 ± 0.37	0.51
Diameter of dominant follicle (mm)	20.4 ± 6.3	20.3 ± 6.1	20.6 ± 5.9	0.98
Endometrial thickness (mm) on the day of hCG triggering	9.09 ± 2.77	8.98 ± 2.97	9.21 ± 2.58	0.64
Mid-luteal Serum progesterone (ng/mL)	10.77 ± 4.49	10.73 ± 4.42	10.82 ± 4.57	0.88

*Number of stimulated cycles till pregnancy occurs or completing the 3 cycles of the study (whichever is earlier).

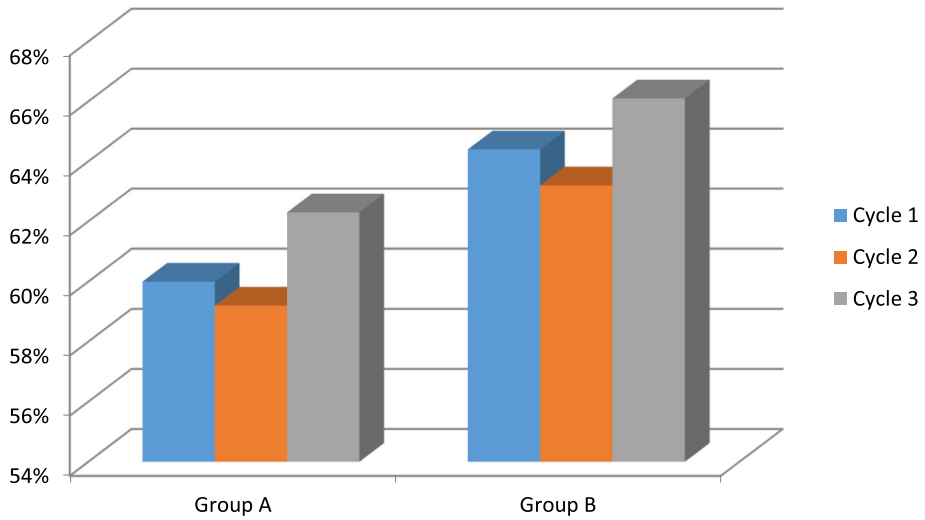

Fig. 2 Cases reaching mature follicular size during the study period

In this study, there were no statistically significant differences (P > 0.05) between the 2 studied groups (Clomiphene Citrate plus CoQ10 versus hMG) regarding the number of cases reaching mature follicular size during the study period (60.0% compared to 64.4% in the first cycle, 59.2% compared to 63.2% in the second cycle, and 62.3% compared to 66.1% in the third cycle). As regard the mean values of mid-luteal serum progesterone, there was no statistically significant difference (P= 0.88) between both groups (10.73 ± 4.42 ng/mL in group A compared to 10.82 ± 4.57 ng/mL in group B).

Regarding the number of pregnancies diagnosed by positive serum pregnancy test, there was no statistically significant difference (P= 0.61) between both groups, with 15 pregnancies achieved in group A (20.0%)) compared to 17 pregnancies (23.3%) in group B. Also, there was no statistically significant difference between both groups as regard the clinical pregnancy rate (P= 0.77) with 14 pregnancies (18.7%) achieved in group A compared to 15 pregnancies (20.5%) in group B.

Several previous studies demonstrated the role of supplementation of CoQ10 in women with PCOS.

El Refaeey et al. studied the effect of CoQ10 supplementation in Clomiphene Citrate resistant PCOS patients and found that ovulation happened in 65.6% of patients (54/82 cycles) in CoQ10 group compared to 15.5% in control group. Clinical pregnancy rate in CoQ10 group was significantly higher as compared to control group (37.3% and 6%, respectively) [20].

Also, Lakshmi et al. studied the effect of adding CoQ10 to Clomiphene Citrate in ovulation induction in PCOS patients and found significantly higher number of

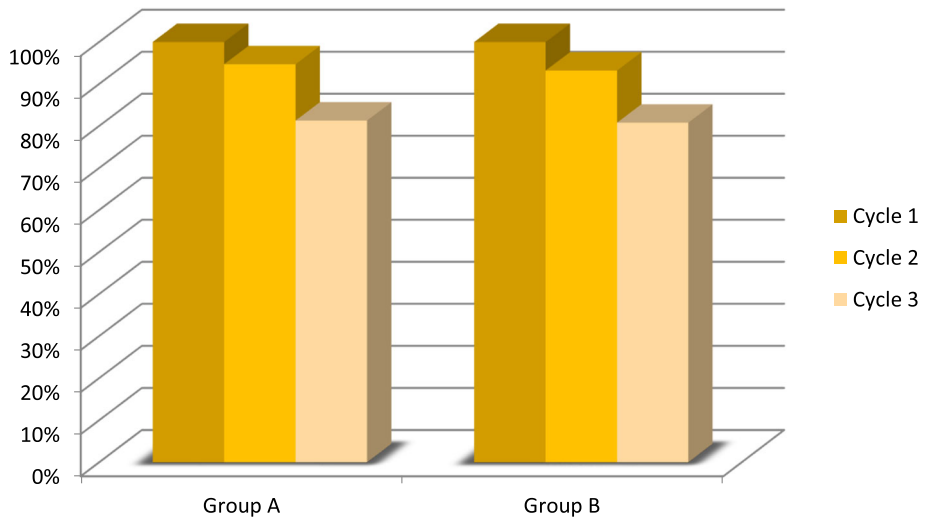

Fig. 3 Number of stimulated cycles during the study period

Table 3 The secondary outcomes

Pregnancy rate	All patients (N=148)	Group A (N=75)	Group B (N=73)	p-value
Cases with positive serum pregnancy test	32 (21.6%)	15 (20.0%)	17 (23.3%)	0.61
Clinical pregnancies	29 (19.6%)	14 (18.7%)	15 (20.5%)	0.77
Multiple pregnancy	6 (4.0%)	2 (2.67%)	4 (5.48%)	0.38
Miscarriages	9 (6.0%)	4/75 (5.33%)	5/73 (6.85%)	0.69

follicles >14 mm and >18 mm in CoQ10 group than control group. Also, they found significantly greater endometrial thickness, higher serum estradiol level and clinical pregnancy in CoQ10 group [25].

Yahya et al. studied the effect of supplementation of either CoQ10 or vitamin D3 for 2 months in Clomiphene Citrate resistant PCOS patients and found that ovulation occurred in 13/17 (76.5%) and clinical pregnancy occurred in 3/17 (17.6%) of patients in CoQ10 group. The overall treatment outcome of both groups in their study has shown that ovulation rate was improved significantly as compared to Clomiphene Citrate alone according to pre-treatment baseline data. Therefore, they concluded that combination of Clomiphene Citrate with either of them seems to be a promising, effective and safe in ovulation induction in Clomiphene Citrate resistant PCOS patients [26].

PEKCAN et al. studied the effect of coenzyme Q10 supplementation on the cumulative pregnancy rate in young infertile PCOS patients with Clomiphene Citrate failure or resistance undergoing ovulation induction and intrauterine insemination (IUI). 130 infertile patients were included in this prospective study and were divided into 2 groups. The study group received CoQ10 (Ubiquinone) 100 mg twice daily for one month. The control group received no treatment. Thereafter, patients underwent ovulation induction (by sequential CC and gonadotropins) and IUI till pregnancy occurred or for 3 months. The authors concluded that short term supplementation of CoQ10 had no therapeutic benefit on the cumulative pregnancy rate. The authors also stated that they had some limitations like the short duration of treatment (only one month of Ubiquinone) and the short follow up time [27].

As far we know, this is the first study to evaluate the beneficial effect of combining the active form of Coenzyme Q10 (Ubiquinol) and Clomiphene Citrate when compared with Human Menopausal Gonadotropins (hMG) in PCOS patients with Clomiphene Citrate resistance.

The achieved clinical pregnancy rate with Ubiquinol / Clomiphene Citrate combination was comparable (P= 0.77) to that achieved in the Human Menopausal Gonadotropins (hMG) group (14 pregnancies in group A compared to 15 pregnancies in group B). Taking into consideration, the disadvantages of hMG stimulated cycles; the required close monitoring of follicular growth, the higher risk of multifetal gestations and ovarian hyperstimulation syndrome and notably the higher price which represents a significant economic burden on the lower economic standard patients who unfortunately had to postpone their treatment cycles because of such

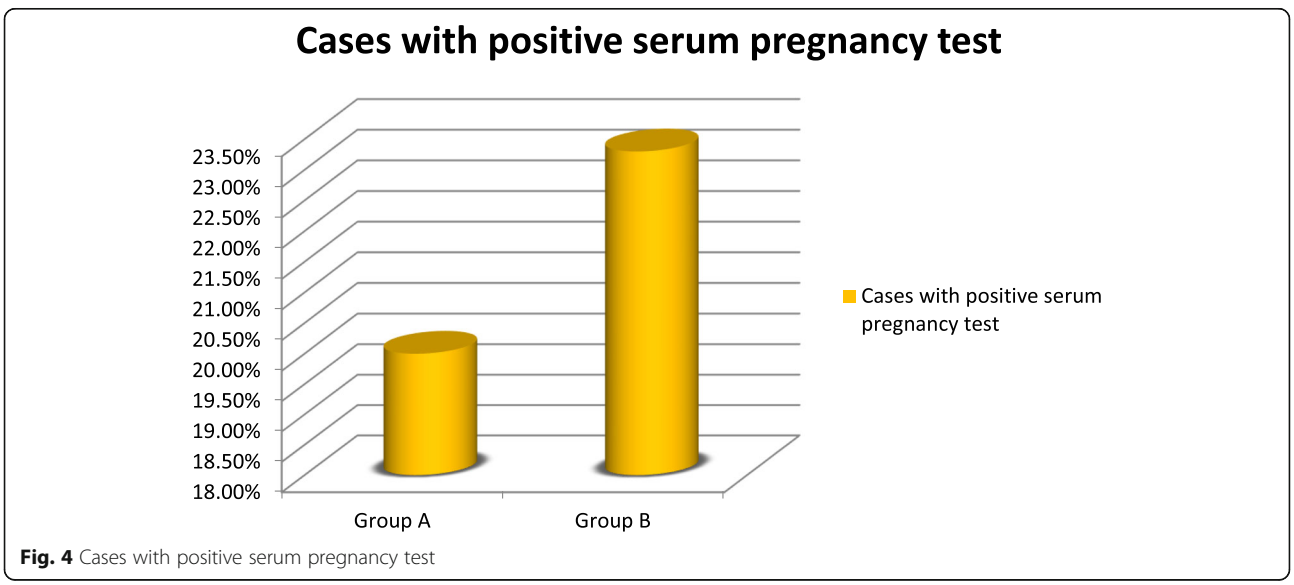

Fig. 4 Cases with positive serum pregnancy test

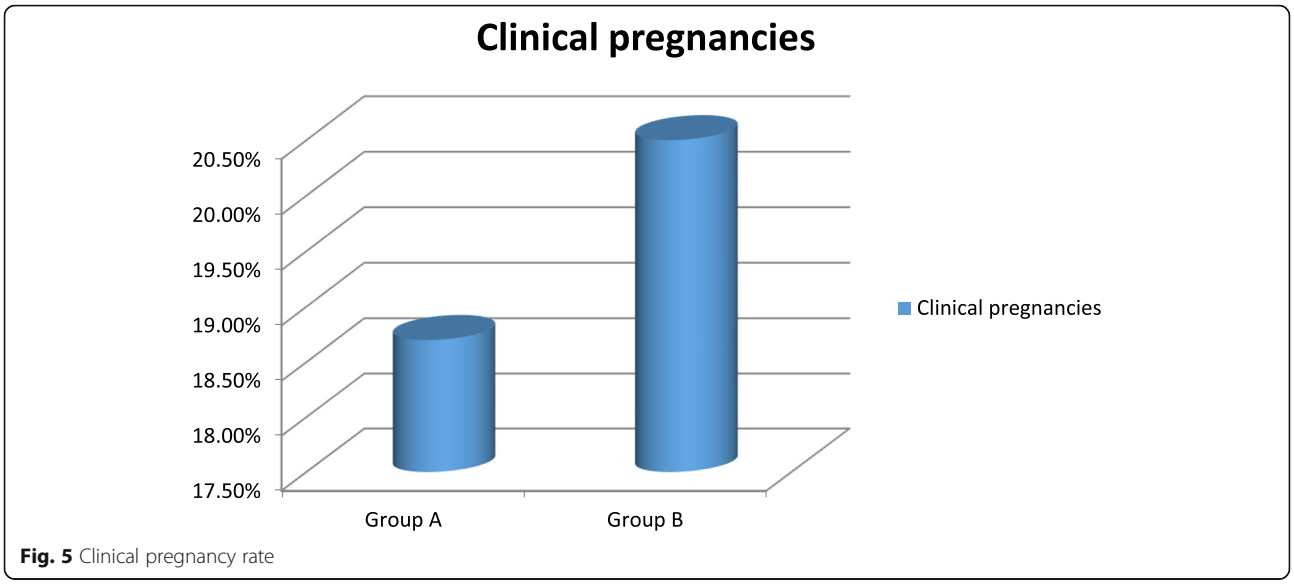

Fig. 5 Clinical pregnancy rate

financial cause [28], we can thereby assume that; Ubiquinol / Clomiphene Citrate combination can be a useful cheaper and safer alternative to the conventional hMG protocol in patients with Clomiphene Citrate resistance.

Limitations of this study

Limitations of this study were; the studied drugs (Clomiphene Citrate, Ubiquinol and Human Menopausal Gonadotropins) were not covered by medical insurance in Saudi Arabia, the need for frequent hospital visits for transvaginal folliculometry and withdrawal of blood samples for serum progesterone assay. Also, we did not follow up the outcome of the ongoing pregnancies.

Conclusions

The addition of the active form of Coenzyme Q10 (Ubiquinol) to Clomiphene Citrate improved the ovarian responsiveness in Clomiphene Citrate resistant patients in terms of follicular growth to the size of mature follicle, number of stimulated cycles, the endometrial thickness on the day of triggering, the luteal function and consecutively the pregnancy rate with results comparable to the conventional hMG stimulation protocol.

Abbreviations

ATP: Adenosine triphosphate; BMI: Body mass index; CC: Clomiphene Citrate; CCR: Clomiphene Citrate resistance; CoQ10: Coenzyme Q10; COS: Controlled ovarian stimulation; ELISA: Enzyme Linked Immunosorbent Assay; FSH: Follicle stimulating hormone; hCG: Human Chorionic Gonadotropin; hMG: Human Menopausal Gonadotropins; HSG: Hysterosalpingography; IR: Insulin resistance; IUI: Intrauterine insemination; LH: Luteinizing hormone; OHSS: Ovarian hyperstimulation syndrome; PCOS: Polycystic ovary syndrome; TVS: Transvaginal ultrasonography

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Availability of data and material

The data that support the findings of this study are available from the corresponding author, (Islam Mohamed Magdi Ammar), upon reasonable request.

Authors' contributions

IMMA: conception and design of study, acquisition of data, and manuscript revision. AMA: analysis of data, manuscript drafting, and manuscript revision. All authors have read and approved the manuscript.

Funding

Not applicable

Declarations

Ethics approval and consent to participate

The Human Research Ethics Committee of the Saudi German Hospital Madinah has approved the study prospectively (Protocol reference number: SGHM-MAR2019-OBGYN) and full ethical approval has been granted. Trial registration: ClinicalTrials.gov Identifier: NCT04870502 (Retrospectively registered on 9/4/2021). Written informed consent was obtained from all patients before participating in the study.

Consent for publication

Not applicable

Competing interests

The authors declare that there are no actual or potential conflicts of interest with respect to research, authorship and/or publication of this article.

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