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Vitamin E supplementation for Infertile Women with Clomiphene Citrate-Resistant Polycystic Ovary Syndrome: Could it Improve Outcome?

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ABSTRACT

Introduction and aim: Polycystic ovary syndrome (PCOS) is a common medical condition and resistance to Clomiphene Citrate (CC) is common. Oxidative stress plays a role in PCOS pathogenesis. Thus, antioxidants could play a role in management. Vitamin E in higher doses did not fully addressed in PCOS. Thus, the current work aimed to evaluate the effects of vitamin-E treatment on ovulation and pregnancy rates in PCOS resistant to CC treatment.

Methodology: This study included 100 women with CC-resistant PCOS. Patient demographics and basal hormonal assay (FSH, LH, prolactin and TSH, were evaluated and recorded. The vitamin E group received 2000 IU/day from metformin starting till the end of the study. Dominant follicles ($\geq$ 18 mm) and endometrial thickness were evaluated by transvaginal ultrasound. The primary outcome was the ovulation and pregnancy rates in each cycle. The secondary outcomes were the number of dominant follicles, the endometrial thickness (ET), and progesterone levels.

Results: The study and control groups showed non-significant differences regarding studied outcomes except significant increase of ET in the study than the control groups (8.82±1.88 vs 7.90±1.74 mm, 9.47±2.11 vs 8.14±1.79 mm, and 9.95±2.39 vs 8.44±1.94 in the first, second and third cycles, successively). In addition, the ovulation rate was significantly increased in the third cycle in the study than the control group (93.2% vs 76.6%, respectively). No significant side effects were recorded.

Conclusion: The use of higher doses of vitamin E improved the ovulation and pregnancy in PCOS women resistant to CC-treatment. However, it did not reach statistical significance. However, it significantly increased endometrium thickness from the first cycles and ovulation rate significantly increased in the third cycle.

Keywords: Vitamin E; Clomiphene Citrate; Polycystic Ovary Syndrome; Resistance; Ovulation.

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common medical condition, encountered in daily obstetric practice. It is the commonest cause of anovulation and account for about 80.0% of PCOS-associated infertility [1]. The standard diagnostic clinical characters of PCOS include anovulation, hyperandrogenism, Acne, hirsutism, and multiple ovarian cysts [2], and the diagnosis could be built upon the revised 2003 Rotterdam criteria [3].

Clomiphene citrate (CC) is the standard and first-line treatment drug to stimulate (induce) ovulation in PCOS women seeking pregnancy [4,5]. Its action is mediated through prevention of negative feedback loop mediated by estrogen at the hypothalamus 5. However, CC-resistance was recorded for up to 40% of PCOS. It is defined as an ovulation failure after treatment by 150 mg of CC daily for 5 days each cycle, for at least three uninterrupted cycles [6,7].

The specific pathogenic mechanisms responsible for CC-resistance in PCOS remains unclear. However, oxidative stress was suggested to play a significant role. It is considered a potential inducer and initiator of PCOS [8,9]. Oxidative stress seems to be included in the altered steroidogenesis, carried out in the ovaries. Thus, androgen production is increased, follicle growth is disturbed with final infertility [10,11]. Furthermore, oxidative stress plays a crucial role in CC-resistance. For example, it exerts anti-estrogenic effect with resultant endometrium [12,13]. Thus, antioxidants (e.g., L-carnitine, [14], N-acetyl cysteine [15,16] could increase ovulation and pregnancy rates in CC-resistant PCOS.

Vitamin E- a lipid soluble vitamin is known as an-antioxidant. It acts by activation of the intracellular antioxidant enzymes and protection of the cellular membrane from an oxidative process known as "lipid peroxidation" [17]. In animal models, feeding female rats with a vitamin-E deficient diet for 70 days, was associated with deterioration of ovulation [18]. Different clinical trials of infertile women (due to diverse causes) revealed that, Vitamin-E supplementation (doses ranged from 100 to 1000 mg/dl) might work as an implantation enhancer and increase pregnancy rates [12,19-22]. However, one recent study by Morsy et al. [23] was not able to support the value of vitamin-E for infertile women with CC-resistant PCOS.

With high safety profile and tolerability [24], vitamin E attracted our attention to evaluate its effects on ovulation, and pregnancy rates, when used with standard PCOS-treatment (CC and metformin) in resistant cases.

PATIENTS AND METHODS

This was a prospective randomized controlled trial. It had been completed between January 2018 and December 2019 (A total of two years). It included 100 women with PCOS, who were recruited from a University Hospital (Damietta Faculty of Medicine, Al-Azhar University) and Damietta General Hospital (Ministry of Health, Egypt).

We used the revised 2003 Rotterdam consensus criteria for the diagnosis of PCOS. The cardinal inclusion criteria, besides PCOS, were infertile females younger than 40 years of age, who had ovulation failure in previous three uninterrupted menstrual cycles with an induction by 150 mg/day of CC for 5 days per cycle. On the other side, female was excluded from the study if she was above 40 years of age, under vitamin or anti-oxidant supplementation for the previous three months, under gonadotropin induction, or had chronic medical diseases (e.g., Diabetes Mellitus, Hypertension, liver or kidney disease, cardiovascular disease, thyroid dysfunction or hyperprolactinemia).

Ethical aspects: The study protocol was reviewed and approved by the local research and ethics committee (DFM, Al-Azhar University, Damietta, Egypt) (IRB00012367-17-10-004). All women participated in the study after signing an informed consent. The study had been completed in accordance with ethical codes for research conduct and reporting of Helsinki declaration.

Methods:

For each woman, a basal hormonal assay (day 3 of spontaneous or progesterone-induced menstruation) including follicle stimulating hormone (FSH), luteinizing hormone (LH) were measured to exclude any other causes of infertility (other than PCOS). Then, women were assigned, by simple randomization method to one of two groups: the study (vitamin-E treated group) or control group (placebo group).

In the study and control groups, each woman received metformin HCl (Cidophage, CID Pharmaceuticals), 500 mg three times a day, starting from the first day menstruation (either of spontaneous or induced) till the end of the study. After 4 weeks of metformin treatment, each woman received clomiphene citrate (150 mg/day) (Clomid, Global Napi Pharmaceuticals) for 5 days, starting from day 3 of menstruation. The vitamin E group vitamin E capsules (Vitamin E, Pharco pharmaceuticals), 2000 IU/day (two tablets/day) from metformin starting till the end of the study. The dose of vitamin E was selected as a doubled dose of the study of **Ledee-Bataille et al.** [25], as they used pentoxifylline (800mg/day) in addition to vitamin-E 1000 IU/day.

At the start of the study, the patient's demographic and clinical characteristics were evaluated and recorded. The number of dominant follicles ($\geq$ 18 mm) and endometrial thickness were evaluated by transvaginal ultrasound at the days 10, 12 and 14 for each cycle. At detection of at least one dominant follicle ($\geq$ 18 mm), the woman received 10000 IU of human chorionic gonadotropin (HCG) by intramuscular injection. Corpus luteum (detected by ultrasound) and serum progesterone (midluteal levels at 21 of menstrual cycle) > 5 ng/ml were used to confirm ovulation. Then, couples were instructed to have a timed intercourse (36 hours) after intramuscular HCG injection. Two weeks later and in absence of menstruation, serum HCG values were measured for diagnosis of pregnancy, and if confirmed, woman was instructed to stop all drugs. When a dominant follicle could not be recognized, the woman was instructed to start a new cycle of ovulation induction in the next month. Three cycles were tried for the purpose of the current work.

Outcome measures:

The primary outcome was the ovulation and pregnancy rate for each cycle. When pregnancy was document, the patient was deducted from the next cycle and rates calculated for the next cycle with women not pregnant in the previous one. The secondary outcome measures were: 1) the number

of dominant follicles detected by ultrasound in each cycle, 2) the endometrial thickness determined on the day of HCG administration, and 3) progesterone at day 21.

Data analysis: The sample size was calculated as a convenient sample. All statistical testes were carried out using the statistical package for social science (SPSS) software package, version 16 (SPSS Inc., Chicago, Illinois, USA). The arithmetic mean (a measure of central tendency) and standard deviation (a measure of dispersion) were used to represent normally distributed numerical variables (median and interquartile range were added when the data were abnormally distributed). Otherwise, the relative frequency and percentages were used to represent the qualitative variables. For continuous variables, the independent sample Student's "*t*"-test was used to compare between two groups. But, Pearson's chi-squared test or its substitute "Fischer's exact test, when indicated" was used to examine association between the categorical variables. All testes were two-sided and *P*value $\leq$ 0.05 was considered significant.

RESULTS

In the current work, we were able to include 50 women with polycystic ovary syndrome resistant to CC-treatment in each group; the study (Vitamin-E supported group) and control group (no vitamin E-support). Their age ranged between 21 and 38 years, while body mass index (BMI) ranged between 23.9 to 35.3 kg/m^2, and the infertility duration ranged between 2 and 7 years. The hormonal profile showed that, FSH ranged between 4.2 to 8.2 mIU/ml, while LH ranged between 8.9 to 14 mIU/ml, and prolactin ranged between 6.10 to 29 ng/ml. Finally, TSH ranged between 0.09 to 5.20 mIU/ml. Both study and control groups were comparable (there was no statistically significant difference) regarding patient demographics or hormonal profile (Table 1).

The study and control groups in the first cycle showed non-significant differences regarding the ovulation rate, pregnancy rate, number of women with dominant follicles, follicular diameter and serum progesterone levels. However, endometrial thickness was significantly increased in the study than the control group (8.82±1.88 vs 7.90±1.74 mm, respectively). The same statistical situation was reported for the second and third cycles. The endometrial thickness was significantly increased in the study than the control group (9.47±2.11 vs 8.14±1.79 mm in the second, and 9.95±2.39 vs 8.44±1.94 in the third cycles, respectively). However, the ovulation rate was significantly increased in the third cycle in the study than the control group (93.2% vs 76.6%, respectively) (Table 2). No significant side effects were reported in the current study.

Table (1): Demographic characteristics and hormonal profile of study population at the start of the study

Variable		Study (n=50)	Control (n=50)	Test	p
Age (years)	Mean±SD; Min. – Max.	26.40±2.47; 34- 35	27.24±3.49; 21 - 38	1.38	0.17
Weight (kg)	Mean±SD; Min. – Max.	74.20±5.08; 64-88	75.38±3.73; 64-84	1.32	0.19
Height (cm)	Mean±SD; Min. – Max.	161.30±2.59; 156-170	161.42±2.23; 158-167	0.25	0.81
BMI (kg/m^2)	Mean±SD; Min. – Max.	28.54±2.22; 23.9-35.3	28.94±1.56; 25.64-32.85	1.03	0.31
Infertility duration (years)	Mean±SD; Min. – Max.	3.22±1.31; 2-7	3.52±1.40; 2-7	1.10	0.27
	Median (IQR)	3 (2)	3 (3)		
FSH (mIU/ml)	Mean±SD; Min. – Max.	6.23±0.71; 4.2-8.2	6.05±0.59; 4.9-7.6	1.39	0.17
LH (mIU/ml)	Mean±SD; Min. – Max.	11.86±0.91; 8.9 - 14	11.61±0.59; 10.40-13.0	1.66	0.10
Prolactin (ng/ml)	Mean±SD; Min. – Max.	14.00±4.86; 6.10 – 27.20	12.90±4.89; 5.80- 29.0	1.13	0.26
TSH (mIU/ml)	Mean±SD; Min. – Max.	2.39±0.84; 0.09- 5.20	2.22±0.77; 0.8-3.90	1.06	0.29

Table (2): Outcome among studied women in the first, second and third cycles

		Study (n=50)	Control (n=50)	Test	p
Cycle 1	Ovulation (n, %)	29 (58.0%)	22(44.0%)	1.96	0.16
	Pregnancy (n, %)	3 (6.0%)	1(2.0%)	FE	0.61
	Patients with Dominant follicles (n, %)	5(10.0%)	3 (6.0%)	FE	0.71
	Follicular diameter (mean±SD)	17.44±3.93	16.41±4.03	0.92	0.36
	Endometrial thickness (mm, mean±SD)	8.82±1.88	7.90±1.74	*2.45*	*0.013**
	Progesterone (ng/ml)	10.44±1.70	10.32±1.45	0.40	0.69
Cycle 2	Ovulation (n, %)	35/47 (74.5%)	31/49 (63.3%)	1.40	0.23
	Pregnancy (n, %)	3(6.4%)	2(4.1%)	FE	0.48
	Patients with Dominant follicles (n, %)	7 (14.9%)	4 (8.2%)	FE	0.35
	Follicular diameter (mean±SD)	17.42±3.13	16.36±2.33	1.60	0.11
	Endometrial thickness (mm, mean±SD)	9.47±2.11	8.14±1.79	*3.32*	*0.001**
	Progesterone (ng/ml)	12.68±1.41	12.38±1.58	0.98	0.33
Cycle 3	Ovulation (n, %)	41/44 (93.2%)	36/47 (76.6%)	*4.80*	*0.028**
	Pregnancy (n, %)	6 (13.6%)	3(6.4%)	FE	0.30
	Patients with Dominant follicles (n, %)	13(31.7%)	10(27.8%)	0.14	0.71
	Follicular diameter (mean±SD)	18.12±3.37	17.44±2.76	0.95	0.34
	Endometrial thickness (mm, mean±SD)	9.95±2.39	8.44±1.94	*3.32*	*0.001**
	Progesterone (ng/ml)	14.93±2.05	14.85±1.89	0.20	0.84

DISCUSSION

Oxidative stress is considered as a main and significant factor in the pathogenesis of polycystic ovary syndrome (PCOS) [14,26]. Thus, antioxidants could play an important role in the management of PCOS. Vitamin-E (as an antioxidant) seems to be important for maintaining of normal ovarian and reproductive function, and protected the ovaries from the oxidative stress exerted by different reactive oxygen species during the process of luteolysis [19,27-29]. Here we aimed to investigate a large dose of vitamin-E on the outcome of ovulation and pregnancy rates among CC-resistant PCOS. The oral dose of 2000 IU/day, is used in the current study, as lower doses were tested before and showed non-significant results. With higher safety profile, we proposed that, increasing dose of vitamin-E could improve the outcome of ovulation induction among CC-resistant PCOS.

The results of the current work showed an improvement in all outcomes in vitamin-E supported group than the control group. However, the difference did not reach statistical significance, except for the endometrial thickness in the first, second and third cycles. In addition, the ovulation rate was significantly increased in the third cycle in the study than the control group (93.2% vs 76.6%, respectively). However, the pregnancy rate did not differ significantly between study and control groups. We could not identify previous randomized controlled studies used vitamin E with the metformin-CC regimen for women with CC-resistant PCOS, except that of Morsy et al. [23]. However, we used higher dose of vitamin-E than their study (2000 IU/day versus 1500 IU/day, respectively). In addition, our study included more women than Morsy et al. [23]. Their results revealed no significant differences between study and control groups regarding ovulation and pregnancy rates, serum midluteal progesterone, number of dominant follicles and mean follicular diameter. Endometrial thickness was significantly higher in the vitamin-E supported than control group. They concluded that, their results could not support the hypothesis of the benefits of vitamin E to increase the ovulation and pregnancy rates in women with CC-resistant PCOS. Our results are in line with these results except in the third cycle where ovulation rate was significantly increased in the study than the control group. the higher number of women in the current work and the higher dose of vitamin-E could explain these results. In addition, it elevates the value of high dose of vitamin E on the ovulation rate. This warrants the future studies on graduated and serial doses of vitamin E to discover the optimal dose which could be helpful for CC-resistant PCOS.

Previous reports used different antioxidants (e.g., L-carnitine, coenzyme Q10 and N-acetyl cysteine) and reported that, these antioxidants had a significant improvement of ovulation and pregnancy rates in CC-resistant PCOS. However, most of these trials did not include metformin in the treatment protocol. Metformin is well-known for its effect on improvement of ovulation in PCOS (69.1% ovulation rate when used alone) [30-33] by a significant reduction of LH in improvement in the regularity of the menstrual cycle [34,35]. This truth could explain the non-significant difference between the study and control groups in the current study, as metformin could mask the effect of vitamin E, and when the women are sensitive or had a contraindication to metformin, vitamin-E seems to be a reasonable and effective alternative. However, the combined use of both metformin and Vitamin E is an optimal technique when the best outcome is desirable.

Previous studies also indicated that, other antioxidants (L-carnitine, coenzyme Q10 and N-acetyl cysteine) exerted their benefits by mechanisms other than antioxidant effects [36-39].

Shokrpour and Asemi [40] used a combination of magnesium (250mg/day) and vitamin E (400 mg/day) for PCOS women for a total duration of 12 weeks and reported that, this combination had benefits for hirsutism, serum high sensitivity reactive protein (hs-CRP), plasma nitric oxide (NO), and total antioxidant capacity (TAC). Ebrahimi et al. [41] and Izadi et al., [37] have proven that vitamin-E supplementation has a significant effect in women with PCOS. It can significantly decrease serum triglycerides (TG) and serum total cholesterol (TC) and improve insulin resistance (IR), Total and free testosterone index in women with PCOS. In addition, Morsy *et al.* [23] confirms the effect of vitamin E can improve the endometrial thickness of CC-resistant PCOS, but had no significant effect on ovulation and pregnancy rates.

The ovulation rate in the current study was high. However, the pregnancy rate is not in line with this higher rate of ovulation. This could be explained by the lower rate of patients with dominant follicles. In addition, other factors could contribute such as the absence of regular sexual intercourse or other male-factors like increased abnormal sperms (count, movement or morphology) [42- 44].

Another important factor for successful pregnancy is the condition of the endometrium at the time of implantation, as the uterus provide the suitable environment (for attachment and nourishment of the fertilized ovum) for the early embryo [45,46]. However, the good endometrial thickness observed in the current work raise the role of other unknown factors, responsible for failure of pregnancy. For example, it is well-known that, PCOS itself is associated with poor development of endometrium (e.g., increased dyssynchrony between endometrial glands and stroma) [47], which could explain lower pregnancy rate due to failed implantation.

The significant increase of endometrium thickness with vitamin E treatment (in the current work) is in line with previous reports. For example, this was attributed to the inhibition of apoptosis and DNA damage by the antioxidant actions of vitamin E [28,44,48].

In 2017, Fatemi *et al.* [20] reported that, the use of vitamin E and D3 significantly increased the thickness of endometrium and was associated with significant increase of pregnancy rates in PCOS women treated by intracytoplasmic sperm injection. However, the higher pregnancy rate could be attributed to the technique of intracytoplasmic sperm injection itself which avoids the abnormal sexual intercourse and semen parameters.

In summary, the current work showed that, the use of higher doses of vitamin E improved the ovulation and pregnancy in PCOS women resistant to CC-treatment. However, it did not reach statistical significance. The significant improvement of endometrium in the supported group reflects the benefits of vitamin E. The use of placebo in the control group increased the value of the current work, as the investigators and patients were blinded and thus the effects could be attributed to the supplemental

use of vitamin E, although it did not show statistical significance. The use of higher dose of vitamin-E also represent a value of the current work. It could be used with future large-scale studies to determine the optimal dose and duration of vitamin-E treatment.

However, the limitation of small included females in both groups, with inclusion of CC-resistant women prevents the generalization of the results of the current work. Future studies on large scale with inclusion of different regimens and groups of PCOS women are highly recommended to reach a final value of vitamin-E in PCOS.

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