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Research Article

Combined N-Acetylcysteine and Clomiphene Citrate for Ovulation Induction in Polycystic Ovary Syndrome, a Double Blind Randomized Controlled Trial

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Abstract

Background: Polycystic ovary syndrome is the commonest endocrinological disorder in women in child bearing period. The PCOS is more prevalent nowadays due to availability of diagnostic tools.

Aim: To evaluate the additive value of N-Acetylcysteine (NAC) to Clomiphene Citrate (CC) on outcome of ovulation induction in women with PCOS.

Patients and Methods: A randomized controlled trial was conducted at Algezeera hospital and Almarwa hospital, Egypt, in the period from April 2018 till January 2019 on 150 infertile women.

Results: There was a statistically significant difference between the case and control group in pregnancy rate with better pregnancy rate in women received NAC together with CC with a P value=0.008 than control group who received CC alone.

Conclusion: NAC when added to CC can enhance ovulation and pregnancy rates in PCOS patients.

Introduction

Women that have polycystic ovary syndrome are more liable to have insulin resistance and obesity [1]. Some women who have PCOS are not obese but have hyperinsulinemia that hinder ovulation because hyperinsulinemia has a vital role in pathophysiology of PCOS through stimulation of secretion of androgen from theca cells of the ovary and inhibit sex hormone binding globulin formation leading to an increase in free androgens. Moreover, hyperinsulinemia changes the pulsatile production of FSH and LH Leading to impairment of ovulation [2]. Unexplained infertility is diagnosed when there are no definite factors that cause infertility [3]. Clomiphine citrate resistance is failure of ovulation after administration of 150 mg of clomiphine citrate for five days in a cycle for at least three treatment cycles this occurs frequenly with obesity, insulin resistance and hyperandrogenemia [4]. N-Acetyl Cysteine (NAC) is the acetylated form of the amino acid L-cysteine. It is a source of sulfhydryl groups and is converted *in vivo* to metabolites that Enhance glutathione secretion, increase detoxification and act as an antioxidant [5].

Patients and Methods

This is a randomized controlled trial that was conducted at Algezeera hospital and Almarwa hospital, Egypt, on 150 infertile women with PCOS.

Inclusion criteria

Women who fulfilled the diagnostic criteria for PCOS, which includes 2 of the following 3 criteria, Hypergonadism, chronic oligomenorrhea or anovulation and polycystic ovarian echopattern [6].

All patients had patent both fallopian tubes confirmed by Hysterosalpingography (HSG). Males of the women included in the study had normal semen profile according to WHO criteria.

Exclusion criteria

Coexistence of other causes of infertility other than anovulatory cause, Thyroid dysfunction, Hyperprolactinemia, congenital adrenal hyperplasia, Cushings syndrome, D.M using medications that interfere with carbohydrate balance.

Consent

All ladies included in the research signed an informed written consent before participating into the study. All women were subjected to full history taking, Full examination, 2 D transvaginal ultrasound on day 2 of the cycle, FSH, LH hormonal essay at day 2 of the cycle.

Randomization

Randomization of cases was done by computer method. 150 women with infertility and have PCOS were enrolled in the study and were distributed in two groups: group 1 and group 2. The randomization allocation was 1:1. The two groups are randomly selected.

Allocation and Concealment

150 opaque envelopes were numbered serially and in each envelope the corresponding letter which donate the allocated group was put according to randomization table then all envelops were closed and put in one box. When the first patient arrives the first envelope was opened and the women were allocated according to the letter inside.

Group 1 received CC 100 mg /dl plus NAC 1.2 g/d, NAC

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Table 1: Demonestrates a comparison between CC+NAC and CC+placebo group as regarding demographic data.

	CC+NAC Group (N= 150)	CC +NAC group (N= 150)	P value	Significance
Age (years) Mean ± SD	26 ± 5.2	26.2 ± 4.9	0.732	NS
Weight (KG) Mean ± SD	74.2 ± 9.7	74.9 ± 9.1	0.52	NS
Height (cm) Range Mean ± SD	159.3 ± 5.8	160 ± 6.2	0.313	NS
BMI Range Mean ± SD	27.8 ± 3.1	28.1 ± 3.2	0.41	NS

NS: Non Significant

Table 2: Demonestrates a comparison between CC+ NAC and CC+ placebo as regarding FSH, LH and FSH/LH ratio.

	CC+NAC Group (N=150)	CC + placebo group (N=150)	P value	Significance
FSH/LH Mean ± SD	6.5 ± 2.2	6.6 ± 2.1	0.687	NS
LH Mean ± SD	7.3 ± 2.1	7.2 ± 2.3	0.649	NS
FSH / LH Mean ± SD	0.8 ± 0.2	0.8 ± 0.3	1	NS

Table 3: Shows a comparison between CC+ NAC and CC+ placebo group as regarding endometrial thickness, number of mature follicles and ovulation rate.

	CC + NAC Group (N= 150)	CC+ placebo Group (N= 150)	P value	Significance
Endometrial thickness Mean ± SD	5.7 ±1.4	5.6 ± 1.2	0.507	NS
Number of dominant			0.676	NS
Follicles				
0	110 (73.3)	118 (78.7)		
1	20 (13.3)	16 (10.7)		
2	12 (8)	8 (5.3)		
3	8 (5.3)	8 (5.3)		
Ovulation rate	60 (40 %)	36 (24%)	0.003	S

Table 4: Comparison between NAC and control group as regard serum progesterone and serum E2.

	CC+ NAC group (N=150)	CC+ placebo Group (N=150)	P value	Significance
Serum progesterone at midluteal phase Mean ± SD	6.7 ± 5.2	4.6 ± 5.1	<0.001	S
Serum E2 36 hours After HCG administration Mean ± SD	152.3 ± 122.4	112.4 ± 121.8	0.005	S

Was administered in the form of powder in a sachet that is diluted in a standard glass of water and administered twice per day while women in group 2, received CC plus a placebo which is an oral rehydration solution powder for five days beginning from day 3 of the cycle.

After that, on day 12 of the cycle, when there is a minimum of one follicle measures ≥18 mm by US, 10000 U HCG was given intramuscularly then timed intercourse was planned 36 hours post injection then B HCG level was measured 2 weeks after HCG injection.

Outcome measures

The primary outcome was to evaluate ovulation rate in the treatment cycles, While the secondary outcomes were, the number of mature follicles ≥18 mm, serum E2 level at ovulation time, 36 hours post injection of HCG, pregnancy rate thickness of endometrium and progesterone concentration at midluteal time. Ongoing pregnancy was referred to as a living pregnancy at least twelve weeks post HCG administration.

Results

The present research was a double blinded randomized controlled trial that was made to assess the value of adding NAC as an adjuvant to CC on induction of ovulation in women with infertility with polycystic ovary syndrome.

The current study has the above mentioned inclusion and exclusion criteria.

We had 150 women who had infertility with PCOS who were randomly distributed into 2 groups.

There was no statistical significant difference between both groups regarding age with a mean ± SD (27 ± 5.7) in CC +NAC group and (25.9 ± 5.9) in group 2 as demonstrated in Table 1.

Also the present study revealed that there is no statistical significant difference between the 2 groups regarding BMI, height and weight as shown in Table 1.

Discussion

In the present study, there was no statistically significant difference between both groups as regard age, weight, BMI, height, FSH, LH and FSH /LH ratio (Table 2).

Transvaginal US examination at day 12 of the cycle, revealed that there were mature folloicles more than 18 mm in about 48 women of the 150 women included in the study. Also there was a highly statistically significant difference in pregnancy rate As 28 women got

Table 5: Shows a comparison between both CC+ NAC group and CC+ placebo as regard pregnancy.

	CC+ NAC Group (N=150)	CC+ placebo Group (N=150)	P value	Significance
Pregnancy	28 (18.7%)	12 (8%)	0.007	S

Table 6: Demonestrates a comparison between CC+ NAC and CC+ placebo group as regard multiple pregnancy and ovarian cyst.

	CC+ NAC Group (N=150)	CC+ placebo group (N=150)	P value	Significance
Multiple pregnancy Twins	4 (2.7%)	0 (0%)		NS
Adverse effects Ovarian cyst	4 (2.7%)	0 (0%)		NS

pregnant in CC+ NAC group whereas only 12 women got pregnant in the control group. A previous research made by salehpour et.al revealed that the ovulation and pregnancy rates were higher in the group who received the CC+ NAC *versus* the control group with statistically significant difference with a P value < 0.002 and 0.04 respectively [7].

The present study is in agreement to a previous study made by salehpour et al., 2012, who performed a randomized controlled trial on 2 groups one received CC+ NAC and the other group received CC and placebo, they found that the mean endometrial thickness was statistically higher in CC+ NAC group with a P value=0.001 [8] (Table 3).

The present study results comes in accordance with a previous study made by badawy et al., who made a study on 537 women who had PCOS and concluded that NAC when added to CC showed significant increase in ovulation rate, serum progesterone and estrogen levels, endometrial thickness and pregnancy rate when compared to clomiphene citrate alone [5] (Table 4).

Also a previous study made by Rizk et al., revealed that NAC+ CC significantly enhanced the ovulation and pregnancy rates in 150 ladies with clomiphene citrate resistant PCOS women [9].

In the current study, the incidence of ovulation in the CC+ NAC group was 40 percent (36 cases out of 150 women) and in CC+ Placebo group was 24% (36 out of 150 women) with a statistically significant difference.

In the present study, the serum level of estradiol and progesterone were statistically significant difference between the 2 groups with a higher levels in the case group *versus* control group, with P values 0.005 and 0.001 respectively

In contrary to the results of our study, a previous research made by Abu Hashim et al., that concluded that combining metformin to CC has a higher efficacy than combining NAC and CC with better ovulation and pregnancy rates and also higher E2 and endometrial thickness [4] (Table 5,6). Where as a previous study made by Youssef et al., showed that there was no statistically significant difference between the group who used NAC and the group who did not receive it regarding pregnancy rates [10].

Conclusion

NAC when added to CC can enhance ovulation and pregnancy rates in PCOS patients.

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Disclosure Statement

All authors declare that there are not any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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