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Research Article

# Adjuvant Use of N-acetyl-cysteine with Clomiphene Citrate in Polycystic Ovary Syndrome after Ovarian Drilling: A Randomized Controlled Trial

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**Abstract**

**Aim:** Evaluate the possible beneficial role of adjuvant use of N-acetyl-cysteine and clomiphene citrate in women with polycystic ovary syndrome after laparoscopic ovarian drilling.

**Methods:** This prospective randomized placebo-controlled double blind clinical trial included 68 women diagnosed with clomiphene citrate resistant polycystic ovary syndrome. After laparoscopic ovarian drilling, they were randomized to either receiving 50 mg oral clomiphene citrate twice daily and oral NAC 1,200mg/day for 5 days starting from cycle day 2 to cycle day 6 (group 1 = 32 patients) or clomiphene citrate only (group 2 = 32 patients).

**Results:** Both biochemical and clinical pregnancy rates were similar in the 2 groups 13/32 (40.6%) in group 1 and 15/32 (46.9%) in group 2 [P = 0.801]. The ovulation rate showed no statistical significant difference between the 2 groups, 24/32 (75%) in group 1 *vs*. 22/32 (68.8%) in group 2 [P = 0.739].

**Conclusion:** N-acetyl-cysteine seems to have a favorable effect on the endometrial thickness when used with clomiphene citrate in women with polycystic ovary syndrome. Yet, there is not an apparent benefit on neither pregnancy nor ovulation rates in clomiphene citrate resistant cases following laparoscopic ovarian drilling.

**Keywords:** Polycystic ovary syndrome; N-acetyl-cysteine; Clomiphene citrate; Clomiphene citrate resistance; Laparoscopic ovarian drilling

## Introduction

Polycystic Ovary Syndrome (PCOS) is considered as one of the most frequent endocrinal disorder among females affecting almost 5-10% of them and is a leading cause of female infertility [1]. Anovulation mainly, together with other factors as increased incidence of miscarriage and obesity, all are conditions that appear to affect reproductive capacity of these women [2].

Clomiphene Citrate (CC) is still considered the first-line treatment for ovulation induction in PCOS [3] with pregnancy rates reaching 36% [4]. CC resistance, defined as failure of ovulation with 150mg CC daily for 5 days for 3 cycles, remains a major problem occurring in almost 40% of PCOS women treated with CC [5]. Insulin resistance, hyper-androgenism, and obesity are major factors incriminated in the process of CC resistance [6].

Laparoscopic Ovarian Drilling (LOD) is a treatment option for anovulatory infertility with CC resistance in PCOS, the resultant reduction of the ovarian stroma and parenchymal blood flow leads to a decrease in ovarian androgen production with subsequent restoration of ovarian-pituitary feedback allowing better ovarian response to gonadotrophin stimulation [7]. Insulin-sensitizing agents, as metformin, have been studied as a treatment option to correct the disorder caused by insulin-resistance [8]. In spite of improved ovulation and clinical pregnancy rates, no improvement was noticed in live birth rates [9].

N-Acetyl Cysteine (NAC), the acetylated precursor of L-cysteine and reduced glutathione [10], is a commonly used mucolytic drug that increases cellular levels of antioxidants and reduces glutathione. NAC potentially improves insulin receptor activity and improves glucose induced insulin secretion [11]. NAC is suggested to have a beneficial role in inducing ovulation in PCOS secondary to its insulin-enhancing effects8. Still, limited number of studies addressed the possible beneficial role of NAC on insulin sensitivity and better outcomes of ovulation induction in women with PCOS [11,12].

This study was conducted to evaluate the possible beneficial role of the adjuvant use of NAC and CC in women with PCOS after LOD.

## Methods

This prospective randomized placebo-controlled double blind clinical trial was conducted in Ain Shams University maternity Hospital from January 2012 to June 2013. Approval of the ethical committee of Department of Obstetrics and Gynecology together with an informed written consent from each patient was obtained before commencement of the study. 68 women diagnosed as PCOS according to the revised 2003 European Society for Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) Rotterdam criteria [13] and confirmed as CC resistant were recruited after exclusion of other causes of




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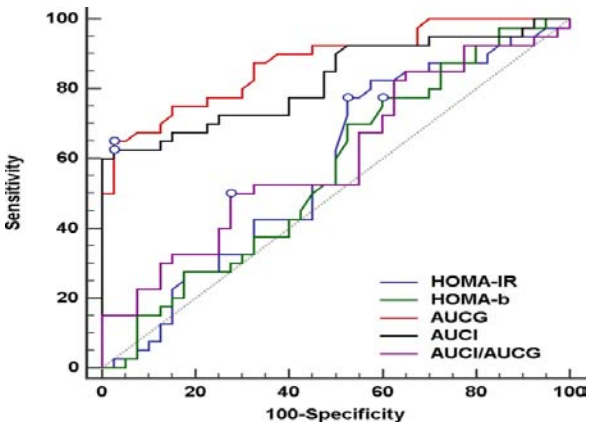


**Figure 1:** ROC Curves for Association between Markers of Insulin Resistance and Recurrent Miscarriage.

**Table 1:** Demographic data of the 2 groups.

| Variables | Group I CC+NAC N=32 | Group II CC+placebo N=32 | P value | Significance |
|---|---|---|---|---|
| **Age (years)** | 25.43±4.1 | 25.7±3.7 | 0.716 | NS |
| **BMI (kg/m²)** | 27.72±2.75 | 28.5±3.34 | 0.063 | NS |
| **Duration of marriage (years)** | 4.32±2.75 | 5.5±3.34 | 0.128 | NS |
| **Duration of infertility (years)** | 3.98±2.7 | 3.11±1.6 | 0.12 | NS |
| **Primary or secondary infertility** | | | | |
| **Primary** | 22(68.8%) | 17(53.1%) | 0.2 | NS |
| **Secondary** | 10(31.3%) | 15(46.9%) | | |
| Data are presented as mean±SD or number (%); NS = Non-significant | | | | |

**Table 2:** Laparoscopic findings in both groups.

| Laparoscopic findings | Group I CC+NAC N=32 | | Group II CC+placebo N=32 | | Chi-square | |
|---|---|---|---|---|---|---|
| | N | % | N | % | $X^2$ | P-value |
| Ovarian PCO & patent both tubes | 29 | 90.7 | 27 | 84.4 | 0.571 | 0.45 |
| Dissected omental adhesions | 0 | 0 | 1 | 3.1 | 1.016 | 0.313 |
| Ovarian cyst aspiration | 0 | 0 | 2 | 6.3 | 2.065 | 0.151 |
| Ovarian adhesions | 0 | 0 | 1 | 3.1 | 1.016 | 0.313 |
| Adhesions bet ovary and tube | 1 | 3.1 | 0 | 0 | 1.016 | 0.313 |
| Unilateral weak spill of dye | 0 | 0 | 1 | 3.1 | 1.016 | 0.313 |
| Para-tubal cyst | 1 | 3.1 | 0 | 0 | 1.016 | 0.313 |
| Subserous myoma | 1 | 3.1 | 0 | 0 | 1.016 | 0.313 |
| Total | 32 | 100 | 32 | 100 | | |

infertility. All patients underwent diagnostic laparoscopy and LOD was done.

Participants were randomized using computer generated list (MedCalc Software Version 13.2.2, Acacialaan 22, B-8400 Ostend, Belgium) into 2 groups. The allocation sequence was concealed from the researchers by using sealed envelopes and the codes were only broken after the data were analyzed. Group 1 (32 female) received 50mg oral CC (Clomid®; Hoechst Marion Russel, Egypt) twice daily and oral NAC 1,200mg/day (2 sachets added to 100ml water, 3 times daily, each sachet contain 200mg (Sedico®, Egypt), for 5 days starting from cycle day 2 to cycle day 6. Group 2 (32 patients) received CC and placebo in the form of sachets identical to NAC sachets containing sugar powder. The flow chart of the study is outlined in Figure 1.

Folliculometry was started (using trans-vaginal ultrasound, Medison, sonoscape A6 model, 6.5 MHz endo-vaginal probe) on day 10 and repeated till at least one follicle ≥18mm where 10,000 IU Human Chorionic Gonadotrophin (HCG) (Choriomon®, IBSA) intramuscular injection was given to trigger ovulation where patients were advised to have intercourse 24 to 36 hours following HCG injection, and then daily for the next 3-4 days. Pregnancy test performed 16 days after HCG injection and ultrasound 3 weeks later to confirm clinical pregnancy. The same course was repeated for another 2 cycles if pregnancy didn't happen. The primary outcome was the biochemical pregnancy rate, and secondary outcomes included Clinical pregnancy rate, ovulation rate, number of follicles ≥ 18mm and endometrial thickness at triggering ovulation, early miscarriage, and side effects.

A previous study showed that adding NAC for CC-resistant women after LOD increased the conception rate from 17/30 (56.7%) to 23/30 (76.7%) [RR 1.4, 95% CI (1.1 to 1.7), p<0.01] [3]. Using EpiInfo®, version 6.0, a minimal sample size of 32 patients in each group is needed to achieve significance of 0.05 and power of 0.8. Statistical analysis was performed using IBM© SPSS© Statistics version 21 (IBM© Corp., Armonk, NY). Categorical data was presented as number (%) or ratio and differences among groups was compared using the Pearson chi-squared test. Normally distributed numerical data was presented as mean (SD). Skewed numerical data was presented as median (inter-quartile range) and between-group differences was compared non-parametrically using the Kruskal Wallis test with application of the Mann-Whitney for pair-wise comparisons if there is a statistically significant difference. P<0.05 was considered statistically significant.

## Results

Sixty four women with PCOS and CC resistance and had LOD done for them were included in the study and randomized to 2 groups, Group 1, received CC and NAC and Group 2, received CC and placebo. No statistical significant difference between both studied groups in demographic data or laparoscopic findings (Table 1, 2). Both biochemical and clinical pregnancy rates were similar and showed no statistical difference between the 2 groups being 13/32 (40.6%) in group 1 (2, 5 and 6 in 1st, 2nd and 3rd cycles respectively) and 15/32 (46.9%) in group 2 (3, 6 and 6 in 1st, 2nd and 3rd cycles respectively) [P = 0.801], with only one twin pregnancy in each group (Table 3). The ovulation rate showed no statistical significant difference between the 2 groups, 24/32 (75%) in group 1 *vs.* 22/32 (68.8%) in group 2 [P = 0.739]. The number of cases with early miscarriage was higher in the placebo group (3 [20%]) than the NAC group (1 [7.7%]) but still failed to reach statistical significance [P = 0.353]. No statistical difference was found between the 2 groups regarding number of mature follicles (≥ 18mm), mean diameter of follicles and endometrial thickness at day of HCG administration (Table 4). Endometrial thickness only showed statistically significant difference in the 3rd cycle. Finally, there was no difference regarding side effects of the prescribed drugs (Table 5).

**Table 3:** Incidence of twin-pregnancy in cases with positive clinical pregnancy.

| Variables | Group I CC+NAC | Group II CC+placebo | P value | Significance |
|---|---|---|---|---|
| | N=13 | N=15 | | |
| Singleton | 12(92.3%) | 14(93.3%) | 0.528 | NS |
| Twins | 1(7.7%) | 1(6.7%) | | |
| Data are presented as number (%); NS = Non-significant | | | | |

**Table 4:** Number of mature follicles (≥ 18mm), mean diameter of follicles and endometrial thickness at day of HCG administration.

| | Group I CC+NAC N=32 | Group II CC+Placebo N=32 | Significance | P value |
|---|---|---|---|---|
| **No. of mature follicles (≥18mm)** | | | | |
| 1st cycle | 5.09±1.2 | 4.75±1.41 | 0.299 | NS |
| 2nd cycle | 5.64±1 | 5.33±0.68 | 0.215 | NS |
| 3rd cycle | 5.75±0.77 | 5.89±0.66 | 0.554 | NS |
| **Diameter (mm)** | | | | |
| 1st cycle | 15.94±3.69 | 15.88±2.86 | 0.94 | NS |
| 2nd cycle | 16.27±2.86 | 16.48±2.59 | 0.79 | NS |
| 3rd cycle | 17.25±2.02 | 16.89±1.91 | 0.597 | NS |
| **Endometrial thickness (mm)** | | | | |
| 1st cycle | 9.09±1.28 | 8.72±0.99 | 0.195 | NS |
| 2nd cycle | 9.86±1.17 | 9.85±0.99 | 0.97 | NS |
| 3rd cycle | 10.56±0.96 | 9.89±0.88 | 0.039* | S |
| Data are presented as mean±SD; NS = Non-significant; S = Significant | | | | |

## Discussion

CC is still considered the 1st line treatment for ovulation induction in anovulatory PCOS; nevertheless, CC resistance remains a major and common problem affecting 15-40% of women with PCOS [4-14]. Few studies in literature have suggested the possible beneficial role of NAC in CC resistant females with PCOS [12,15], to our knowledge, only one study addressed this beneficial role after LOD [3]. This study was conducted to assess the role of NAC in ovulation induction in females with CC resistant PCOS after LOD.

This study could not find any clinical superiority for NAC over placebo regarding pregnancy rate, both biochemical and clinical, ovulation rate, number of dominant follicles (≥ 18mm) or mean diameter of follicles. These results are in contrary to the results of the previously mentioned study which found a significant improvement in both pregnancy and ovulation rates compared to placebo [77% *vs.* 57% (RR 1.4; 95% CI 1.1-2.7) and 87% *vs.* 67% (RR 1.3; 95% CI, 1.2-2.7) respectively, P < 0.01], and a significant increase in number of dominant follicles (2.9 *vs.* 1.8, P < 0.05) when compared to placebo group [3]. Our study only agreed with Nasr's study on the beneficial effect of NAC on improving endometrial thickness when used as an adjuvant to CC, an observation agreed upon by most researchers [15-17] apart from a single study who did not find a significant change in endometrial thickness when using NAC with CC [12]. This controversy of results between the 2 studies could be attributed to the long follow up (12 cycles) used in the other study. Another difference in the setting of this study was the bilateral LOD used rather than unilateral LOD used in the other study.

**Table 5:** Side effects of prescribed drugs.

| Side effect | Group I CC+NAC N=32 | | Group II CC+placebo N=32 | | P-value | Significance |
|---|---|---|---|---|---|---|
| | N | % | N | % | | |
| Headache | 1 | 3 | 2 | 6 | 0.554 | NS |
| Blurring of vision | 0 | 0 | 1 | 3 | 0.313 | NS |
| Abdominal pain | 1 | 3 | 1 | 3 | 1 | NS |
| Dryness during intercourse | 0 | 0 | 2 | 6 | 0.151 | NS |

Despite the few studies in literature addressing the role of NAC in PCOS, conflicting results have been reported about the value of this drug. The randomized study conducted by Rizk et al. (2005) was the only study demonstrating the beneficial role of NAC in women with CC resistant PCOS, they reported marked increase in both pregnancy and ovulation rates [21.3% *vs.* 0% and 49.3% *vs.* 1.3% respectively, (P = 0.00006, P < 0.0001)] [12]. The other randomized trial which suggested this beneficial role was conducted after unilateral LOD [3]. The other 3 studies suggesting the significant improvement of both pregnancy and ovulation rates with the adjuvant use of NAC, conducted their studies on PCOS women without CC resistance.

Just as studies suggested this beneficial role of NAC in CC resistant PCOS, others have failed to demonstrate this role. A prospective controlled pilot study conducted on 39 CC resistant PCOS, failed to find any statistical difference regarding the clinical pregnancy rate [P = 0.24] [18]. Another 2 randomized controlled trials assessing the value of NAC in CC resistant PCOS, found no significant value in improving neither pregnancy nor ovulation rates. They suggested that the adjuvant use of metformin with CC would be more beneficial for these patients [ovulation rates were 51.6% (16/31) *vs.* 6.7% (2/30) in one study and the ovulation and pregnancy rates were (69.1% *vs.* 20.0%, P = 0.002, and 22.7% *vs.* 5.3%, P = 0.020, respectively in the other study)] [10,18]. The results of this study support the evidence against use of NAC in women with CC resistant PCOS. Furthermore, the high pregnancy (77%) and ovulation (87%) rates assumed by Nasr (2010) can be attributed to the LAD rather than the use of NAC [3]. This idea is supported by the results of this study which also showed also similarly high pregnancy (40.6%) and ovulation rates (75%) when compared to other trials using NAC in CC resistant PCOS not preceded by LAD (21.3% and 5.3% pregnancy rates, respectively) [12,18] and (6.7%, 49.3% and 20.0% ovulation rates, respectively) [10,12,18].

## Conclusion

NAC seems to have a favorable effect on the endometrial thickness when used with CC in women with PCOS. Yet, the level of evidence supporting its adjuvant use with CC in CC resistant PCOS remains weak, further larger randomized controlled trials should address this issue. Very limited studies addressed the incidence of live birth rates, which was not addressed in this study, also longer duration of follow up including more ovulation trial cycles should be addressed to validate the results of some studies. Also, a larger randomized trial should be conducted on the use of NAC following LOD in CC resistant women to validate the conflicting results of the 2 to date trials addressing this issue.

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