

N-acetyl-cysteine in anovulatory women: The impact of postcoital test

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ABSTRACT

Objective: N-acetyl-cysteine (NAC), a mucolytic drug with insulin sensitizing properties, has been proved useful as an adjuvant therapy in subjects with polycystic ovary syndrome (PCOS) resistant to clomiphene citrate (CC). The objective is to determine the possible beneficial mucolytic effect of NAC on patients with poor post-coital tests.

Design: Prospective, controlled pilot study.

Materials and methods: Thirty-nine women diagnosed with CC-resistant PCOS, aged 17 – 42 years undergoing therapy for infertility were included. All women were given NAC (1.2 g/d) and with CC 100 mg/d for 5 days starting at day 3 of the cycle. They were divided according to the results of their priori post-coital test into: good post-coital test (Group I: N=11) and poor post-coital test (group II: N=28).

Main Outcome Measure(s): Clinical pregnancy rate (CPR).

Result(s): There were no demographic differences (i.e. age, period of infertility, weight, previous use of CC) between the two groups, nor differences in the cycle characteristics (i.e. cycle length, ovulation induction, number of follicles produced). In addition, there was no statistical difference between the two groups pertaining the clinical pregnancy rate ($P = 0.24$).

Conclusion: The sample size of the present study is not large enough to withdraw firm conclusions, but we may assume that the effect of NAC as an adjuvant to CC appears not to be related to its mucolytic effect.

Key Words: N-acetyl-cysteine, polycystic ovary syndrome, clomiphene citrate resistance, post-coital test, pregnancy

N-acetyl-cysteine (NAC), a safe and cheap drug available in the market many years ago, was found to have a role in infertility management (1). It was proved useful as an adjuvant therapy in subjects with polycystic ovary syndrome (PCOS) resistant to clomiphene citrate (CC). Combination of CC and NAC significantly increased both ovulation rate and pregnancy rate in women with CC resistant PCOS (49.3% vs. 1.3 and 21.3% vs. 0% respectively) (2).

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NAC has multiple biological effects (3) Two of them are potentially and directly related to improved pregnancy rate. It has mucolytic action, thus can counteract the negative influence of clomiphene Citrate on cervical mucous (4). In the same time has insulin sensitizing effect that could help in cases with PCOS (5, 6).

Therefore, is the beneficial effect of NAC due to its Insulin sensitizing effect, or its mucolytic effect? The aim of the present study is to evaluate the efficiency of using a combination of CC and NAC in a cohort of women undergoing intrauterine insemination (IUI) according to the results of a priori post-coital test.

MATERIALS AND METHODS

The present study was prospectively conducted in the Department of Obstetrics, Cairo during the period from September 2004 through December 2005. Thirty-nine women diagnosed with CC-resistant PCOS (no ovulation despite CC 150 mg for three cycles), aged 17 – 46 years undergoing therapy for infertility were included and consent was obtained after counseling. Participants were divided according to the results of their post-coital test into: good post-coital test (Group I: N=28) and poor post-coital test (group II: N=11) 'poor despite normal semen analysis (Table 1).

The postcoital test was planned 14-16 days before menstruation and 6-18 hours after intercourse. The couples were asked to have intercourse as usual on the night before the test; no instructions were on prior abstinence, postcoital rest, or posture. A non-lubricated speculum was used to expose the cervix. Endocervical mucus was collected by suction in a narrow 1 ml disposable syringe. Mucus was considered to be good if it was abundant (0.3 ml), highly ductile (100 mm), and mostly clear to the naked eye.

The number of sperms moving forward per high power field ($\times 400$ magnification) was recorded. A negative or abnormal ("absent" or "non-motile") sperm result was considered valid only if the mucus was in good condition or if the test had been repeated and timed by ultrasonic measurement of follicles and serum estradiol concentration in a later cycle.

Table 1. Criteria of Good and poor postcoital test

Postcoital test results	
Good:	* Normal amounts of sperm are seen in the sample. * Sperm are moving forward through the cervical mucus.
Poor:	* The mucus stretches at least 2 in.(5 cm). * Mucus cannot stretch 2 in.(5 cm). * No sperm or a large percentage of dead sperm is seen in the sample. * Sperm are clumped.

Table 2. Different characteristics and outcomes of both groups

	Good PCT	Poor PCT	P value		
Number	28	11			
Age (years)	27.07	5.11	30.45	6.39	P= 0.06
Infertility (years)	1.70	1.19	1.63	3.89	P= 0.5
Weight (Kg)	80.11	16.59	84.55	13.04	P= 0.22
Cycle length (days)	35.64	12.78	34.55	6.49	P= 0.38
Ovulation	96.43%		72.73%		P= 0.06
Follicles	1.46	0.79	1.36	1.21	P= 0.38
Pregnancy	42.86%		27.27%		P= 0.24
Tolerance	92.9%		91.1%		P=0.64

Results are presented in mean \pm SD

These two parameters (mucous and sperm) were the two fundamental factors for assessing postcoital test as used by other investigators as well (7).

All participants received a combination of clomiphene citrate 100 mg from cycle day 3–7 and NAC (Sedico, Cairo, ARE) for the same duration, in a dose of 1.2 g/day orally. Monitoring of the cycle included transvaginal determination of the mean follicular diameter and Human chorionic gonadotropin was administered when at least one follicle measured 18 mm.

Timed intercourse was advised 24-36 hours after hCG injection. A serum progesterone level was checked 6-8 days after the administration of hCG. A serum hCG level was determined 14 days after hCG injection if menses had not yet occurred. Pregnancy was defined as a rise in the serum hCG level. All women's data were recorded in a special input form and analyzed at the end of the study. Statistical significance was defined by P values of 0.05 or less. Statistical analysis was performed with SAS 8.2 (SAS Inc., Cary, North Carolina).

RESULTS

There was no difference in the background characteristics of those with poor or good post coital test regarding age, infertility duration, weight, and cycle length (Table 1).

Monitoring for ovulation showed no statistically significant difference between both

groups regarding ovulation rate or number of follicles growing although ovulation was higher in the group with good PCT. NAC was tolerable by almost all cases. Pregnancy was achieved in 12 cases in Group I and 3 cases in group II. (Odds ratio = 0.63 lower limit = 0.09 and upper limit = 3.07 (Table 2).

DISCUSSION

The negative influence of clomiphene citrate on cervical mucus can create a "hostile" environment for conception. It was studied previously in many centers allover the world. In one study, women underwent randomized alternate cyclical treatment with either 100 mg CC, or with placebo. The effect of CC and placebo on serum estradiol (E2), cervical mucus secretion and on the development of ovarian follicles was evaluated. Compared with placebo, treatment with CC significantly increased the number of mature ovarian follicles on the day of assumed ovulation (p less than 0.05), elevated E2 secretion (p less than 0.05) and decreased cervical score (p less than 0.05). It can be concluded that anti-estrogenic agents reduced the secretion of cervical mucus (8). Not only this but sperm-mucus penetration test score was also affected by use of CC (in spontaneous cycles was 11.4 (95% CI 7.6 to 15.2) and in CC cycles 3.9 (95% CI 1.17 to 6.63) (9). This was further supported by other investigators (10, 11).

The post-coital test (PCT) could provide a generally applicable test of sperm mucous penetration. It dates back to 1866 and is widely used in infertility investigations (12, 13).

An abnormal PCT in the presence of normal semen is considered to reflect cervical hostility (14). The post-coital test requires no expensive equipment and a negative PCT reduced the cumulative chance of conception at 24 months after first attending an infertility clinic almost four-fold (15).

Accordingly, in the present study we hypothesized that the mucolytic effect of N-Acetyl cysteine would overcome the anti-estrogenic hostile effect of clomiphene citrate and explain the higher pregnancy rate with combined

NAC-CC (2). The ovulation rate and number of follicles were not significantly different. However, the effect on conception rate was also not different suggesting that its effect on mucus was not the factor crucial for conception to achieve. This matches well with other investigators who tried to improve conception rate by improving cervical mucus quality (16).

The sample size of the present study is not large enough to withdraw firm conclusions, but we may assume that the effect of NAC as an adjuvant to CC appear not to be related to its mucolytic effect.

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