Clomiphene citrate plus N-acetyl cysteine versus clomiphene citrate for augmenting ovulation in the management of unexplained infertility: a randomized double-blind controlled trial

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Objective: To compare clomiphene citrate with N-acetyl cysteine vs. clomiphene citrate alone for augmenting ovulation in management of unexplained infertility.

Design: Prospective randomized double-blind controlled trial.

Setting: Department of obstetrics and gynecology in a university medical faculty in Egypt.

Patient(s): Four hundred four patients as a study group (clomiphene citrate plus N-acetyl cysteine group) and 400 patients as a control group (clomiphene citrate–alone group). All women had unexplained infertility.

Intervention(s): Patients in the study group were treated with clomiphene citrate (50-mg tablets) twice per day and with N-acetyl cysteine (1,200 mg/d orally) for 5 days starting on day 2 of the cycle. Patients in the control group were treated with clomiphene citrate with sugar powder.

Main Outcome Measure(s): The primary outcomes were number and size of growing follicles, serum E2, serum P, and endometrial thickness. The secondary outcome was the occurrence of pregnancy.

Result(s): There were no statistically significant differences between the two groups in the number of follicles sized >18 mm, mean E2 levels, serum P, or endometrial thickness. Pregnancy rate was comparable in both groups (22.2% vs. 27%). Miscarriage rate was comparable in both groups (6.7% in the study group vs. 7.4% in the control group).

Conclusion(s): N-Acetyl cysteine is ineffective in inducing or augmenting ovulation in patients with unexplained infertility and cannot be recommended as an adjuvant to clomiphene citrate in such patients. (Fertil Steril 2006; 86:647–50. ©2006 by American Society for Reproductive Medicine.)

Key Words: N-Acetyl cysteine, clomiphene citrate, unexplained infertility
soura, Egypt) for management of primary subfertility problems during the period from October 2003 to April 2005. All women had at least 1 year of continuous marriage without conception. They all had had the preliminary investigations for infertility performed and had proved normal. They had patent fallopian tubes as proven by hysterosalpingography; had normal ovulating cycles as proven by midluteal serum P levels; and had normal laparoscopic findings, in addition to normal semen analysis for their partners according to the modified criteria of the World Health Organization. Therefore, by definition, all women had unexplained infertility.

All patients underwent superovulation with normal timed intercourse as a line of management of their problem. All women were included in the study after we had obtained written informed consent, and the study was approved by the ethical committee of Mansoura University. Patients were allocated randomly to either the study group (404 women) or the control group (400 women) using sealed envelopes. Patients in the study group were treated with clomiphene citrate (50-mg tablets twice daily; Hoechst Marion Russel, Arab Republic of Egypt) for 5 days, starting on the 2nd day of the menstrual cycle, and with N-acetyl cysteine (1,200 mg/d orally; Sedico-Cairo, ARE), for 5 days, starting on the 2nd day of the cycle. Patients in the control group were treated with clomiphene citrate in the same dose, in combination with sugar powder, which was used at the same volume as that of NAC, starting on day 2, for 5 days. Patients in the study and control groups were blinded to the real drug and placebo.

Cycles were monitored by transvaginal ultrasound for the mean follicular volume and thickness of the endometrium on days 10, 12, and 14 of the cycle. Serum E2 assay by RIA was performed at the time of hCG injection; serum P was measured between day 21 and day 23 of the cycle by RIA by using the antibody coated-tube method (Coat-A-Count; Diagnostic Product Corporation, Los Angeles, CA). Both radiologist and laboratory personnel also were blinded to the study and placebo group. Injection of hCG was given when ≥1 follicle measured ≥18 mm. Patients were advised to have intercourse 24–36 hours after the hCG injection. Serum hCG was determined 2 weeks after the hCG injection, in the absence of menstruation, for diagnosis of pregnancy.

Treatment was continued to one cycle. The primary outcome measures were the following: number of growing follicles sized >18 mm in the ovary, serum E2 levels, serum P levels, and endometrial thickness. The secondary outcome measure was the occurrence of pregnancy.

Data obtained were statistically analyzed using the SPSS computer package (SPSS, Inc., Chicago, IL) and Fisher’s exact test to compare differences in rates and Student’s t test to assess differences in parametric data. A value of $P<.05$ was considered significant.

**RESULTS**

The study included 804 patients in total. There were no statistically significant differences between the two groups regarding age, duration of infertility, body weight, height, and body mass index (Table 1). There were no statistically significant differences between the two groups in the number of follicles sized >18 mm in both ovaries, mean E2 levels at the time of hCG injection, serum P levels in days 21 to 23 of the cycle, or the endometrial thickness. Pregnancy rate was comparable in both groups (Table 2). There were no cases of ovarian hyperstimulation syndrome. There were 8 cases of twin pregnancy in the study group (8.9%), and there were 12 cases in the control group (11.1%) with no higher order pregnancies. Miscarriage rate was comparable in both groups (6.7% in the study group vs. 7.4% in the control group).

**DISCUSSION**

N-Acetyl cysteine recently has been proposed as an adjuvant to the clomiphene citrate in inducing or augmenting ovulation in different situations (3, 4). N-Acetyl cysteine is a potent antioxidant. Most of the beneficial effects of orally administered NAC are theorized to be due to its ability to either reduce extracellular cystine to cysteine or to be a

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n = 404)</th>
<th>Group 2 (n = 400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>27.9 ± 4.2</td>
<td>28.1 ± 3.7</td>
</tr>
<tr>
<td>Infertility (y)</td>
<td>5.1 ± 2.9</td>
<td>4.3 ± 2.7</td>
</tr>
<tr>
<td>Height (m)</td>
<td>168.0 ± 4.9</td>
<td>161.3 ± 5.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.9 ± 6.2</td>
<td>81.3 ± 5.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5 ± 3.4</td>
<td>26.1 ± 3.1</td>
</tr>
<tr>
<td>Serum FSH (IU/mL)</td>
<td>4.3 ± 2.1</td>
<td>4.6 ± 2.2</td>
</tr>
</tbody>
</table>

Note: $P>.05$ for all characteristics, group 1 vs. group 2. All data are mean ± SD. BMI = body mass index.

source of sulfhydryl metabolites. As a source of sulfhydryl groups, NAC can stimulate glutathione synthesis, enhance glutathione-S-transferase activity, promote detoxification, and act directly on reactive oxidant radicals (26).

\[ \text{N-Acetyl cysteine} \]

N-Acetyl cysteine is used primarily as a mucolytic drug, but it has been proven effective for many other uses, such as to promote detoxification, to enhance the effects of nitroglycerin on the heart, to serve as a hepatoprotectant, to lower lipoprotein levels, and to lower homocysteine levels. N-Acetyl cysteine is a safe drug, and its LD50 is very high. Animal studies proved that the drug is neither teratogenic nor mutagenic (27, 28). Overdose of the drug causes minimal allergy, especially after IV administration, and there are no contraindications for its use, apart from known hypersensitivity to the NAC (29). None of the patients in this study reported any side effects from the use of the drug. We had no ovarian hyperstimulations and only 20 multiple pregnancies in the study and control groups. Miscarriage rate was not higher than expected in spontaneous pregnancy.

N-Acetyl cysteine is a very promising drug. Studies have established many possible mechanisms of action to it that might be beneficial in augmenting ovulation. Borgstrom et al. (18) demonstrated the insulin-sensitizing activity of NAC. Other investigators have shown the value of NAC in patients with polycystic ovarian syndrome through its action on hyperinsulinemia and insulin resistance (19–21). Many other mechanisms have been proposed, such as antiapoptotic effects (1, 23). Apoptosis is responsible for the process of follicular atresia. N-Acetyl cysteine was found to inhibit apoptosis in cultured ovarian primordial germ cells. It also preserves vascular integrity, lowers serum homocysteine levels, and is protective against ischemic injuries (17, 24, 27, 30). N-Acetyl cysteine is immunologically active; it has an anticytokine effect and inflammatory-modulating capacity (25).

In the present study, however, NAC was proven to be ineffective in improving the ovulation or pregnancy rates in the study cohort. N-Acetyl cysteine did not add to the ovulatory effect of the clomiphene citrate, and moreover, the results even were better in its absence. These results are different from those that others were reporting (3). Kleinveld et al. (30) reported that in healthy individuals, NAC may act as a pro-oxidant and may lower the glutathione and increase the amount of oxidized glutathione. Although NAC is reported to be a novel beneficial adjuvant to the clomiphene citrate in inducing and augmenting ovulation in polycystic ovarian disease, this was not the case in women with unexplained infertility. In women with polycystic ovary syndrome, insulin resistance is a frequent finding (31, 32), and serum homocysteine is significantly higher than in nonpolycystic patients, which might indicate a role for the use of NAC.

We reported another beneficial effect of NAC when combined with clomiphene citrate; the latter adversely affects the cervical mucus. N-Acetyl cysteine is mucolytic and therefore usually improves the character of the cervical mucus without the need for an estrogen supply. Further studies are required on a larger cohort of women to prove these effects, to compare the efficacy of NAC vs. other insulin-sensitizing drugs, and to assess the effect of NAC on short- and long-term complications of polycystic ovary disease.

In view of the results of the present study, NAC has proved ineffective in inducing or augmenting ovulation in nonpolycystic ovarian disease and cannot be recommended as an adjuvant to clomiphene citrate in such a situation.

**REFERENCES**


