

Comparison of Clomiphene Citrate Plus N-Acetyl Cysteine and Clomiphene Citrate Alone for Induction of Ovulation in Polycystic Ovary Syndrome

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ABSTRACT

Aim: To compare the frequency of ovulation with clomiphene citrate plus N-acetyl cysteine versus clomiphene citrate alone in married females presenting with polycystic ovarian syndrome.

Study design: Randomized clinical trial

Place and duration of study: Department of Obstetrics and Gynaecology, Unit-3 Jinnah Hospital, Lahore from 1st September 2018 to 28th February 2019.

Methodology: A total of 60 patients (30 in each group) were enrolled. In group A, females were prescribed clomiphene citrate 50-mg tablets twice daily with N-acetyl cysteine 1200 mg/day orally for 5 days starting on day 3 of the menstrual cycle and in group B, females were prescribed clomiphene citrate 50-mg tablets twice daily.

Results: Patients ranged between 18-35 years of age. Mean age of the patients was 28.5±3.3 and 28.1±3.1 years in group A and B, respectively. Mean duration of marriage in group A was 3.4±0.9 and in group B 3.5±0.9 year. Mean BMI in group-A was 3.4±0.9 while in group-B 3.5±0.9 (kg/m²). Ovulation was observed at 1st month in group A was 12 (40%) and in group B 9 (30%). Ovulation was observed at 2nd month in group A was 16 (53.3%) and in group B 13 (43.3%). In 3rd months ovulation was seen in 19 patients (63.3%) of group A and 18 patients (60%) of group B. Stratification for age and BMI was also carried out.

Conclusion: This study could not find any clinical superiority for clomiphene citrate plus N-acetyl cysteine versus clomiphene citrate alone in term of ovulation rate.

Keywords: N-acetyl cysteine, Polycystic ovary syndrome, Ovulation induction

INTRODUCTION

Polycystic ovarian syndrome (PCOS) constitutes a continuum spectrum of symptoms starting from early prepubertal years and continuing after menopause and disease expression varies from person to person. To a great extent, etiology of PCOS remained unknown even though synthesis of high androgen levels and insulin resistance were found to be essentially involved in pathophysiology.¹

Clomiphene citrate (CC) was the gold standard drug for the ovulation induction in PCOS, but clomiphene citrate resistance is still seen approximately 15-40%.^{2,3} While CC is the first line of treatment in women with PCOS for chronic anovulation, failure to ovulate is frequent after 150mg/day is received.⁴

N-acetyl cysteine (NAC), a safe and cheap medication that was available several years ago in the market as a mucolytic agent and an alternative to the toxicity of acetaminophen, played an important role in the treatment of infertility. In some recent studies, the potential beneficial effects of NAC on ovulation were discussed. The biological characteristics of NAC make this drug a potential candidate for use in the treatment of infertility, particularly in the PCOS for ovulation inducing or increasing.^{2,3} N-acetyl cysteine is a healthy and tolerated CC adjuvant. In PCOS patients, it increases follicular maturation and pregnancy.⁵

One randomized study found that after the addition of NAC (52.1%), ovulation rates were substantially increased compared to CC alone (17.9%).⁶ Another study showed that women with PCOS, the combination of clomiphene citrate and NAC substantially increased the ovulation rate (49.3%) as compared to clomiphene citrate alone (1.3%).⁷

The rationale of this study is to equate the frequency of ovulation with clomiphene citrate plus NAC versus clomiphene citrate alone in females presenting with PCOS. Literature shows that the addition of NAC to CC will contribute to a higher rate of ovulation compared to CC alone. However, little work has been done in this respect. Local data in literature is also sparse. We therefore want to undertake this study to verify the effectiveness of NAC as well as CC in the local community. In future, we can plan better management protocols to improve the outcome of fertility. This will help to improving our practice as well as updating local guidelines through this study.

MATERIALS AND METHODS

This randomized clinical trial was conducted at Department of Obstetrics and Gynaecology, Unit-3 Jinnah Hospital, Lahore from 1st September 2018 to 28th February 2019 and comprised 60 cases (30 cases in each group). Married females of age 18-35 years, presenting with PCOS and primary infertility were included. Permission was granted from hospital Ethical Committee for this research. All females with secondary infertility and chronic systemic problems like hypertension (BP >140/90 mmHg), diabetes

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(BSR >180mg/dl) were excluded. Demographic information (name, age, duration of marriage and BMI) was obtained. Then females were randomly divided in two groups by using lottery method. In group A, females were prescribed clomiphene citrate 50-mg tablets twice daily with N-acetyl cysteine 1200 mg/day orally for 5 days starting on day 3 of the menstrual cycle. In group B, females were prescribed clomiphene citrate 50mg tablets twice daily only. Then females were followed-up in OPD for 3 months (cycles). On each follow-up visit, females were screened for ovulation by using trans-abdominal ultrasonography. If ≥ 2 mature follicles of size >18mm was present, then ovulation was labelled. All this information was recorded. Data were analyzed by SPSS version 20. Both groups were compared by using Chi-square test for ovulation. P-value<0.05 was considered as significant.

RESULTS

Patients ranged between 18-35 years of age. Mean age of the patients was 28.5 ± 3.3 and 28.1 ± 3.1 years in group A and B, respectively. Mean duration of marriage in group A was 3.4 ± 0.9 and in group B 3.5 ± 0.9 year. Mean BMI in group A was 3.4 ± 0.9 while in group B 3.5 ± 0.9 (kg/m²). Ovulation was observed at 1st month in group A was 12 (40%) and in group B 9 (30%). This was observed at 2nd month in group A was 16 (53.3%) and in group B 13 (43.3%). In 3rd months ovulation was seen in 19 patients (63.3%) of group A and 18 patients (60%) of group B (Tables 1-6).

Table 1: Distribution of patients by age

Age (years)	Clomiphene 50mg with acetyl cysteine		Clomiphene 50mg alone	
	No.	%	No.	%
18-25	4	13.3	6	20.0
26-35	26	86.7	24	80.0
Mean \pm SD	28.5 \pm 3.3		28.1 \pm 3.1	

Table 2: Distribution of patients by duration of marriage

Duration of marriage (years)	Clomiphene 50mg with acetyl cysteine		Clomiphene 50mg alone	
	No.	%	No.	%
≤ 3	16	53.3	16	53.3
≥ 4	14	46.7	14	46.7
Mean \pm SD	3.4 \pm 0.9		3.5 \pm 0.9	

Table 3: Distribution of patients by body mass index

Body mass index (kg/m ²)	Clomiphene 50mg with acetyl cysteine		Clomiphene 50mg alone	
	No.	%	No.	%
≤ 30	25	83.3	26	86.7
> 30	5	16.7	4	13.3
Mean \pm SD	24.4 \pm 1.8		22.5 \pm 2.7	

Table 4: Distribution of patients by 1st month ovulation

Ovulation	Clomiphene 50mg with acetyl cysteine		Clomiphene 50mg alone	
	No.	%	No.	%
Yes	12	40.0	9	30.0
No	18	60.0	21	70.0

Chi square = 0.659 P value = 0.417

Table 5: Distribution of patients by 2nd month ovulation (n=60)

Ovulation	Clomiphene 50mg with acetyl cysteine		Clomiphene 50mg alone	
	No.	%	No.	%
Yes	16	53.3	13	43.3
No	14	46.7	17	56.7

Chi square = 0.601 P value = 0.438

Table 6: Distribution of patients by 3rd month ovulation

Ovulation	Clomiphene 50mg with acetyl cysteine		Clomiphene 50mg alone	
	No.	%	No.	%
Yes	19	63.3	18	60.0
No	11	36.7	12	40.0

Chi square = 0.601 P value = 0.791

DISCUSSION

The first choice of treatment for induction of ovulation in anovulatory women with PCOS remains clomiphene citrate. Cost of medication is low, the oral route administration is patient friendly, relatively few adverse effects are observed, tracking ovarian response is low and abundant clinical evidence on drug safety is available. The mechanism of action is unknown, but the blocking of the negative feedback mechanism is supposed to lead to greater follicle-stimulating hormone secretion (FSH). Obesity, hyperandrogenemia and age are the major variables predicting treatment outcomes. Ovarian volume and menstrual status also contribute to the prediction of CC reactivity⁸.

N-acetyl cysteine (NAC) is the amino acid L-cysteine acetylated form. It is an excellent source of sulfhydryls and in vivo is converted into metabolite which stimulates the development of glutathione, encourages detoxification and acts as free-radical scavengers. Historically, NAC, a mucolytic in a variety of respiratory disorders, but in other conditions such as HIV infection, cancer, heart disease, smoking, severe metal poisoning, prevention of influenza, epilepsy and acetaminophen poisoning. N-acetyl cysteine tends to be helpful inside the body, NAC has various behaviors. It is mainly a strong antioxidant; it works in pancreatic cells for the secretion of insulin and in human erythrocytes for insulin receptors. NAC has antiapoptotic effects; vascular integrity can be preserved and immunological activity can be observed.⁹

This study showed a slightly better rate of ovulation (statistically non-significant) compared to the 1st month (40% versus 30%; $p=0.417$) versus clomiphene citrate alone for the 2nd month (53.3% compared with 43.3%; $p=0.438$) and the 2nd month (63.5% versus 60%; $p=0.791$).

The only randomized research carried out by Rizk et al⁷ showed the useful effect of NAC in women with CC resistant PCOS and showed significant increase in both pregnancy and ovulation (21.3% versus 0%, and 49.3% versus 1.3%, respectively ($P=0.00006$, $P<0.0001$)).

Elnashar et al¹⁰ showed that NAC is not an effective treatment for the induction of ovulation in CC resistant PCOS patients, but another research from Badawy et al⁶ reported that addition of NAC to a CC regimen in PCOS patients would significantly increase ovulation levels compared to placebo.

The patients who received NAC after unilateral laparoscopic ovarian drilling have seen substantial increase in ovulation, pregnancy rates and improved reproductive effects.¹¹

Conflict of interest: None

CONCLUSION

The study found no clinical superiority in clomiphene citrate plus N-acetyl cysteine over ovulation-related clomiphene citrate alone.

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