

Efficacy of N Acetylcysteine as an adjunct to Clomipene citrate in induction of ovulation in Anovulatory Infertility

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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 infertility due to anovulation associated with polycystic ovarian syndrome. The objective of the present study is to determine the possible beneficial effect of NAC and to develop a rationale to its use in such cases as an adjunct to clomiphene citrate (CC) which remains the gold standard for ovulation induction.

Material and Methods: In this placebo-controlled clinical study, 90 patients with anovulatory PCOS related infertility were randomly divided into two groups for induction of ovulation. Patients in group 1 received CC 50/day for 5 days plus NAC 1.2g/d and patients in group 2 received CC only for 5 days starting at day 3 of the cycle. On the 12th day of the menstrual cycle in the presence of at least one follicle with an 18 diameter in ultrasound evaluation, 5000U hCG was injected intramuscularly and timed intercourse was advised 36h after hCG injection. Serum β -hCG level was measured on the 16th day after hCG injection.

Results: The number of follicles >18mm and the mean endometrial thickness on the day of hCG administration were significantly higher among the CC+NAC group (P -value=0.001). The ovulation and pregnancy rates were also significantly higher in the CC+NAC group (P -value=0.02 and 0.001, respectively). No adverse side-effects and no cases of ovarian hyperstimulation syndrome were observed in the group receiving NAC.

Conclusion: NAC as an adjuvant to CC for induction of ovulation can improve the ovulation and pregnancy rates in PCOS patients and may also have some beneficial impacts on endometrial thickness. NAC is well-tolerated, safe, and inexpensive and may be a novel adjuvant treatment to improve the induction of ovulation outcomes in PCOS patients.

Index Terms- acetyl cysteine, clomiphene citrate, polycystic ovaries, anovulation

I. INTRODUCTION

Anovulation is the cause of infertility in about a third of couples attending infertility clinics, and polycystic ovary syndrome accounts for 90% of such cases.¹ Once tests have excluded other causes of androgen excess and menstrual disturbance, the syndrome can be confirmed by the presence of two of the following criteria— biochemical or clinical hyperandrogenism (hirsutism, acne, or alopecia); menstrual

irregularity; and polycystic ovaries². Polycystic ovary syndrome (PCOS) occurs in 5 to 10% of women. One of the main causes of chronic anovulation in the women of reproductive age is polycystic ovary syndrome³. Infertility is defined as the state of nulliparity within one year of unprotected coitus.⁴ The pathogenesis of polycystic ovary syndrome is unknown; however, TGF1 activity on solo ovary cells and peripheral tissues causes a number of clinical and biochemical features such as hyperandrogenism, insulin resistance, increased secretion of adrenal and chronic anovulation⁵

Clomiphene citrate (CC) has been the gold-standard drug for ovulation induction in polycystic ovary syndrome (PCOS), but still CC resistance is seen in approximately 15-40% in women with PCOS. Clomiphene citrate (CC) remains the treatment of first choice for induction of ovulation in anovulatory women with PCOS. Cost of medication is low, the oral route of administration is patient friendly, there are relatively few adverse effects, little ovarian response monitoring is required, and abundant clinical data are available regarding safety of the drug.⁶

N-acetyl cysteine (NAC), a safe and cheap drug available in the market many years ago as mucolytic agent, was found to have a role in infertility management⁷ N-acetyl cysteine is the acetylated variant of the amino acid L-cysteine. It is an excellent source of sulfhydryl groups. It is primarily a powerful antioxidant; it has activity on insulin secretion in pancreatic cells and on insulin receptors on human erythrocytes. NAC has antiapoptotic effects; it can preserve vascular integrity and has immunological functions⁸. NAC has multiple biological effects. 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 mucous⁹. In the same time has insulin sensitizing effect that could help in cases with PCOS^{10,11}. In recent years a limited number of studies has shown the possible benefits of NAC administration in improving insulin sensitivity and better induction of ovulation outcomes in patients with PCOS^{11,12}. Therefore, the present study was undertaken to evaluate the effect of NAC administration as an adjuvant to CC on ovulation and pregnancy rates as compared CC alone in patients with PCOS related anovulatory infertility.

II. MATERIALS AND METHODS

The present study was conducted in a Department of Obstetrics and Gynaecology in Sheri-I-Kashmir Medical college Hospital, Government lalla Ded Hospital Kashmir, and private

infertility practice between June 2015 and June 2016. A total of 90 subjects affected by PCOS, aged 18–37 years were enrolled into study. As described elsewhere¹³, PCOS was diagnosed by a finding of bilaterally normal or enlarged ovaries (ovarian volume 12 cm³) with the presence of at least 7–10 peripheral cysts per ovary. Inclusion criteria include: patients aged less than 37 years, women with PCOS who have 2 criteria from the 3 criteria of Rotterdam (Aovulation; Hyperandrogenemia, hirsutism and acne; Observing polycystic ovary in sonography), normal semen analysis and tubal patency documented by hysterosalpingography. Exclusion criteria: infertility associated with non PCOD cause, tubal block, hyperprolactinemia, thyroid dysfunction and a severe increase in androgen due to adrenal causes. On the 3rd day of the menstrual cycle (spontaneous or progesterone induced) a baseline vaginal ultrasound examination and serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone and thyrotropin (TSH) and prolactin levels were done to match the baseline variables among two groups. The subjects were divided into two

groups, of 45 patients each. Group 1 received a combination of clomiphene citrate 50 mg per day from cycle day 3–7 and NAC for the same duration, in a dose of 1.2 g/day orally. Group 2 received only CC therapy for the same duration. Monitoring of the treatment results included transvaginal determination of the mean follicular diameter. Human chorionic gonadotropin 5000 units was administered when at least one follicle measured 18 mm. A serum progesterone level was checked at day 21 of cycle. A serum hCG level was determined to confirm pregnancy 14 days after hCG injection if menses had not yet occurred. Pregnancy was defined as a rise in the serum hCG level. The primary outcome was the ovulation rate in the treatment cycle. Secondary outcomes included number of follicles of 18 mm, serum progesterone levels, endometrial thickness and subsequent pregnancy rates.

III. OBSERVATIONS

Table 1:

Variable	Group 1(CC+NAC)	Group 2(CC)	P value
Age in yr	27.41±0.41	27.22±3.32	NS
Duration of infertility in yr	3.29±1.86	3.35±2.12	NS
Weight in kg	79.9±5.2	82.3±4.4	NS
BMI	30.1 ±3.1	30.5±2.6	NS
Ovulation rate	20(44.44%)	13(29.00%)	0.02
Endometrial thickness in mm	8.2±1.1	6.4±0.6	<0.001
Follicles >18mm	1.6±0.9	1.1±0.2	<0.001
Serum progesterone ng/ml	6.23±7.6	3.1±2.2	<0.001
Pregnancy rates	21	14	<0.001

There was no difference in the background characteristics between the both groups, as regards age, BMI duration of infertility and weight. As illustrated in the Table 1, All women in the study were in the age range between 18 and 37 years with a mean of 27.22±3.32, the average age of the first and the second group was 27.41±0.41 and 27.22±3.32 respectively. Therefore there was no significant statistical difference observed between the two groups. In group 1, after intake of therapy, the average number of ovarian follicles was 1.6±0.9 and in group 2, it was 1.1±0.2. Further the mean increase in size was 0.9 in the first and 0.2 in the second group, giving a p value of 0.001 which is statistically significant. Further the endometrial thickness and the number of follicles achieving a size of more than 18mm on the expected day of HCG administration were significantly higher in the group 1 as compared to group 2 (p <0.001). In Group 1, the ovulation rate was 44% as compared to 29% in Group 2 which was statistically significant. The pregnancy rates were also statistically and significantly higher in group 1 (21 subjects) as compared to Group 2 (14 subjects). One subject in group 1 had twin pregnancy, 1 subject in each group was lost to follow up, and no case of ovarian hyperstimulation was reported. No other major adverse side effects were noted in both groups.

Accordingly, in the above prospective study we concluded that the mucolytic effect of NAcetyl cysteine would overcome the antiestrogenic hostile effect of clomiphene citrate and explain the higher pregnancy rate with combined NAC-CC. The

ovulation rate and number of follicles were significantly higher in the study group who received combined ovulation induction with clomiphene citrate plus N acetylcysteine. Although, both the ovulation and pregnancy rates were higher in this group but it had a better and more pronounced effect in improving the ovulation rates. The sample size of the present study though not large enough to withdraw definite conclusions, but we may assume that the effect of NAC as an adjuvant to CC appears to be beneficial.

IV. CONCLUSION

In conclusion, based on our study in well chosen subjects, NAC as an adjuvant to CC for induction of ovulation can improve the ovulation and pregnancy rates in PCOS patients and may also have some beneficial impacts on endometrial thickness. NAC is well-tolerated, safe, and inexpensive and may be a novel adjuvant treatment to improve the induction of ovulation outcomes in PCOS patients. NAC exerts its effect due to its mucolytic and metabolic actions especially insulin sensitising effect.

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