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Comparative study of Clomiphene Citrate VS Clomiphene Citrate + N-acetyl Cysteine in Polycystic ovarian disease patient.

KEYWORDS

CC: Clomiphene citrate, NAC: N-Acetyl cysteine. PCOD: Polycystic ovarian disease.

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ABSTRACT **OBJECTIVE –** To evaluate the effect of N-acetyl cysteine, a mucolytic drug with insulin sensitizing properties as an adjuvant therapy in patients of PCOD.**MATERIALS AND METHODS-** One hundred women diagnosed with PCOD, aged between 18-39 years undergoing therapy for infertility were included, patients were randomly assigned to receive either N-acetyl cysteine 1.2 gm/d (group I) or placebo (group II) with clomiphene citrate 100mg/d for 5 days. Starting at day 3 of the cycle. Outcome was measured as ovulation rate and pregnancy rate. **RESULT –** Combination of Clomiphene citrate and N-acetyl cysteine significantly increases both ovulation rate (92.4% Vs 58%) and pregnancy rate (14% Vs 4%). **CONCLUSION: -** The acetyl cysteine as an adjuvant to Clomiphene citrate was more effective than placebo for patients with PCOS.

Polycystic ovary syndrome (PCOS) affects up to 10% of women of reproductive age, in which there is hyperandrogenism, enlarged cystic ovaries, and chronic anovulation often co-exists with obesity, hyperinsulinemia & insulin resistance. Hyperinsulinemia is seen in > 50% of patients with polycystic ovarian syndrome.

Clomiphene citrate has variable success rate in anovulatory women, it has lowest success rate in women with insulin resistance. Various insulin sensitizers are being used for ovulation induction but not all cases respond to insulin sensitizers.

A promising agent is N-acetyl cysteine (NAC). It is safe and well tolerated mucolytic drug that softens tenacious mucous secretions. The peak plasma level of NAC is attained 1 hour after an oral dose and it disappears from plasma after 12 hrs. The biological activity of NAC is attributed to its sulfahydryl group, which enhances glutathione S-transferase activity aiding in the protection of all cells and membranes.

MATERIALS & METHODS:-

The present study was conducted in a medical college based hospital in Bhagalpur between Jan 2016 – Dec 2016. It was conducted over hundred women affected by PCOD (polycystic ovarian disease) aged 18-39 years. PCOS is described as finding of bilaterally normal or enlarged ovaries (ovarian volume > 12cm3) with the presence of at-least 7-10 peripheral cysts per ovary. All patients had at least one tube patent. The patient's male partner underwent a semen analysis and the results were determined to be adequate according to the latest WHO guidelines. The body mass index (BMI) was calculated according to the following formula. Body weight in (kilograms) / height in (m2) obesity were defined as BMI > 30 kg/m2. Informed consent was obtained from each patient before the entry into the study.

PROTOCOL: Amenorrheic patients began treatment with induction of menses using medroxy progesterone acetate 10 mg. twice daily for 5 days. On day three each patient underwent a baseline USG examination. Clomiphene Citrate 100 mg was given from day 3 until day 7. In addition to this CC, each patient was selected randomly to receive either NAC in a dose of 1.2 g/dl, orally or a placebo of the same volume twice daily from day 3 until day 7.

Monitoring of the cycle included transvaginal determination of the mean follicular diameter and measurement of Serum E2 levels. Monitoring intervals were determined by patient response. Human chorionic gonadotropin was administered when at-least one follicle measured 18 mm & the E2 level had increased. A serum Progesterone level was checked on cycle days 21-22. A serum HCG levels was determined 14 days after hCG injection if menses had not yet occurred. Pregnancy was defined as an increase in the serum hCG level on serial determination at least 2 days apart.

RANDOMISATION AND BLINDING

In both groups patients were randomised to receive CC and either NAC or placebo using sealed envelope. Each participant had only one treatment cycle. The patients and the physician monitoring the cycles were blinded to the identity of each medication.

OUTCOME MEASURES:

The primary outcome was the ovulation rate in the treatment cycle. Secondary outcomes included Pregnancy rate (PR), no of follicles ≥ 18 mm, the serum E2 concentration, serum progesterone and endometrial thickness.

STATICAL ANALYSIS:

The proportion of pregnancies that occurred in each group was compared with Fisher's test.

RESULT:

A total of 100 patients were randomised (NAC-50, placebo – 50) in a total of 100cc cycles. As shown in table 1. There was no difference in age, infertility duration, BMI, weight /height, and in FSH / LH during the cycles in which NAC or placebo was given.

The mean E2 levels and the number of follicles > 18 mm at the time of hCG administration in the NAC (N-acetyl cysteine) group was significantly higher than the placebo group. Similarly, significantly higher ovulation rate as well as pregnancy rate was noted in the NAC group.

COMPARISION OF THE CLINICAL COUTCOMES OF THE TWO GROUPS. N= 50.

VARIABLE	GROUP-I, (NAC + CC)	GROUP II (PLACEBO + CC)
Age	18-39	18-39
Duration of infertility	<5 Yrs	<5 Yrs
BMI	30 ±2.6	30 ± 3.1
LH/FSH ratio	3.2	3.1
Fasting insulin (U/ ml)	18.8 ± 4.6	17.8 ± 4.4
Fasting glucose (mg/dl)	80.9 ± 12.6	82.6 ± 14.1
E2 at the time of hCG.(Pg/ml)	400 ± 360.5	200 ± 115.6

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Ovulation rate	46.2%	29%
Follicles > 18 mm.	2.4 ± 0.97	0.8 ± 0.6
Endometrial thickness	5.9 ± 0.6	4.8 ± 1.5
Pregnancy.	7	2

DISCUSSION:

Insulin resistance is a cause of CC failure in patients with PCOS, not only in obese but in lean patients as well. In addition hyperinsulinemia might influence ovarian as well as adrenal steroidogenesis. Consequently insulin lowering drugs were proved effective in the treatment of patients with PCOS. Besides its insulin-sensitizing effect N-acetyl cysteine treatment induced a significant decrease in the Testosterone levels and in free androgen index values. More recently it has also been shown to have other diverse biological effects notably, antiapoptotic, antioxidant, protection against focal ischemia, inhibition of phospholipids metabolism, pro inflammatory cytokine release and protease activity. The NAC (N-acetyl cysteine) may exert the same effect at the ovarian level and these activities may be as important as its insulin – enhancing effect in inducing ovulation.

In the current study, NAC was well tolerated by all the patients and no adverse ffects were observed. I obtained a significant increase of both ovulation and pregnancy rated in the N-acetyl cysteine group. The magnitude of the observed clinical changes is significant from a clinical point of view, especially when compared with previously reported data about the use of metformin or troglitazone. The antiapoptotic effects of N-acetyl cysteine may be responsible for the significantly higher number of follicles in the N-acetyl cysteine group compared to placebo. Its protective effects against ischemic insults as well as its inflammatory – modulating capacity may be the contributory mechanism added to its positive reproductive effects.

CONCLUSION:

N-acetyl cysteine may be a novel adjuvant treatment for patients with polycystic ovarian syndrome. It is simple, well tolerated and inexpensive agent. It could be used as an alternative to other insulin sensitizing agents like metformin or troglitazone.

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