

Comparative Study of Clomiphene Citrate + Metformin and Clomiphene Citrate + N-Acetylcysteine in the Treatment of Infertile Women with Poly Cystic Ovarian Syndrome.

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Abstract

Introduction: Polycystic ovarian syndrome (PCOS) is a hormonal disorder common among women of reproductive age group. Women with PCOS may have infrequent or prolonged menstrual periods or excess male hormone (Androgen) levels. The ovaries may develop numerous small cysts on the outer edges. Polycystic ovarian syndrome affects up to almost 27 % of women during their childbearing years. Metformin is most commonly used in a dose between 500-1500mg/d. Now a day combination of Clomiphene Citrate + Metformin are more effective than combination of Clomiphene Citrate + N-acetyl cysteine for ovulation induction.

Objective: The study was undertaken to compare the efficacy of Clomiphene Citrate + Metformin in one group and Clomiphene Citrate + N-acetylcysteine in the other group in PCOS patients.

Materials and Methods: It was an observational study on 35 patients each in Clomiphene Citrate + Metformin group and Clomiphene Citrate + N acetylcysteine group. The study was conducted in the 70 cases and the effects were evaluated at 12 weeks. For monitoring the effects of the drug various parameters were evaluated for 3 cycles. They included number of follicles, size of follicles, endometrial thickness and rate of conception between the two groups.

Results: In all cycles mean number of follicle, mean size of follicle, Endometrium thickness and rate of conception in group A were significantly higher than that of Group B (P<0.01)

Conclusion: Number of follicles, size of follicles, endometrial thickness and rate of conception was better in group treated with CC+ Metformin as compared to group treated with CC+ N-Acetyl cysteine.

Keywords: Clomiphene citrate, Metformin, N-Acetyl cysteine, PCOS [Polycystic Ovarian Syndrome]

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Introduction

Polycystic ovarian syndrome is characterized by excessive androgen production by the ovaries thereby interfering with the reproductive, endocrine and metabolic functions. PCOS is a multi-factorial & polygenic disorder. The prevalence varies between 4-8%. PCOS is the most common endocrine abnormality in young female reproductive age group. PCOS was originally described in 1935 by Stein & Leventhal as a syndrome manifested by amenorrhea, hirsutism, obesity and enlarged polycystic ovaries. The prevalence of PCOS has increased with the advanced increase of different diagnostic criteria and has been shown to be, $11.9 \pm 2.4\%$ - $17.8 \pm 2.8\%$, based on Rotterdam diagnostic criteria [1]

Diagnosis is based on the presence of any two of the following three criteria oligo-ovulation or anovulation, clinical/ Biochemical evidence of hyperandrogenism and polycystic ovaries on ultrasound assessment with exclusion of disorders such as congenital Adrenal Hyperplasia, Androgen secreting tumors or Cushing syndrome (O.C Dutta 5th) Typically ovaries are enlarged with presence of multiple follicles (>12) measuring about 2-9mm in diameter which are crowded around the cortex making a necklace appearance. Several methods have been effective for ovulation induction and infertility treatment in women with PCOS. This includes weight loss, exercise and lifestyle modification. Drug therapy with Clomiphene Citrate, Metformin Gonadotropins and N-acetylcysteine are effective in patient with PCOS. [2] Insulin resistance is a major associated problem in patients of Polycystic Ovarian Syndrome. Metformin is most commonly used in a dose between 500-1500mg/day. Now a days, N-acetyl cysteine (mucolytic drug). has been tried in conjunction with Clomiphene Citrate

for ovulation induction. Clomiphene Citrate is a non-steroidal fertility drug. It acts on the pituitary gland to release hormone needed to stimulate ovulation. Dose 100 mg/d starting from day 3-7 of menstrual cycle. It blocks the effect of the oestrogen in body. This blocking effect increase levels of other hormones that are essential for ovulation These hormones are FSH & LH.

Metformin: It acts by improving the sensitivity of peripheral tissue to insulin. It is used in PCOS to reduce insulin resistance, improve menstrual regularity with significant reduction in body weight. [3]

N-acetylcysteine: It is a derivative of the amino acid L-cysteine an essential precursor used by the body to produce glutathione. It is both an antioxidant and amino acid. It is also known as NAC. Women with PCOS who have insulin resistance may take NAC as nutritional supplement. It decreases body mass index, hirsutism, Free testosterone and menstrual irregularity. [4]

Aim and Objective:

Polycystic Ovarian Syndrome is a disorder involving infrequent, irregular or prolonged menstrual periods. Earlier many studies have been done with different drugs for their comparative safety and efficacy in the management of Polycystic Ovarian Syndrome. Through our study, We aim to compare the efficacy and safety of Clomiphene Citrate +Metformin and Clomiphene Citrate +N-acetyl cysteine.

Materials and Methods:

This prospective, randomized, open, comparative observational study was conducted in department of Pharmacology, PMCH Patna, This was 12 weeks study between 22 December 2020 to 16 March 2021

in 70 PCOS patients of Age ranging between 18-37 years in patients visiting outdoor, Obstetrics & Gynaecology Department, Patna Medical College and Hospital (PMCH), Patna were taken.

The following categories of patients were enrolled in the study.

Inclusion Criteria

1. All patients of primary and secondary infertility with PCOS
2. Patients with no comorbidity.
3. Written and informed consent form was taken from each patient before the start of study.

The following categories of patients were excluded from the study.

Exclusion Criteria

Infertility due to male factor, Tubal factor and Endometriosis.

Patients were randomly distributed into two groups each of 35 patients.

Group A- comprised of patients receiving Clomiphene Citrate (100 mg/d), starting from day 3-7 of menstrual cycle + Metformin(1000 mg/d).

Group B - Comprised of patients receiving Clomiphene Citrate(100mg/d) from day 3-7 of the menstrual cycle + N-Acetyl cysteine (1,200 mg/d) for 3 month. Ultrasound was performed on day 12 of menstrual cycle to look for number and size of ovarian follicle and endometrial response. This was carried for 3 cycles and number of follicle, size of follicles, endometrial thickness and rate of conception was compared between the two groups

Results

Table 1: Age distribution of patients in the two groups.

Characteristics	Group A	Group B
Age (Years, Mean)	25.24±4.44	26.04±3.01

Table 2: Mean number of follicle of the patients in different cycle in the two group

Mean number of follicle	1 st cycle			2 nd cycle			3 rd cycle		
	Group A	Group B	P. Value	Group A	Group B	P. Value	Group A	Group B	P. Value
Mean±SD	1.36 ± .063	0.80 ± 0.40	P<0.01	1.35 ± 0.49	1.04 ± 0.21	P<0.01	1.61 ± 0.50	1.20 ± 0.42	P<0.01

In all cycles mean number of follicle in group A was significantly higher than that of Group B (P<0.01).

Table 3: Mean size of follicle of the Patients in different cycles in the two group.

Mean size of follicle	1 st cycle			2 nd cycle			3 rd cycle		
	Group A	Group B	P. Value	Group A	Group B	P. Value	Group A	Group B	P. Value
Mean±SD	19.55 ± .159	17.40 ± 1.09	P<0.01	19.59 ± 1.37	17.27 ± 0.88	P<0.01	19.10 ± 1.73	16.60 ± 0.96	P<0.01

In all cycles mean size of follicle in group A was significantly higher than that of Group B (P<0.01)

Table 4: Mean Endometrium thickness' (ET) of the Patient in different cycles in the two Group.

Mean ET	1 st cycle			2 nd cycle			3 rd cycle		
	Group A	Group B	P. Value	Group A	Group B	P. Value	Group A	Group B	P. Value
Mean±SD	6.74 ± 0.79	6.00 ± 0.61	P<0.01	6.79 ± 0.79	6.20 ± 0.39	P<0.01	6.88 ± 1.04	6.20 ± 0.67	P<0.01

In all cycles mean Endometrium thickness' (ET) in Group A was significantly higher than that of Group B (P< 0.01)

Table 5: Conception per patient in the Two group. Group A Group B

	Group A	Group B	P. Value
No. of Conception	11/25 (44.00%)	6/25 (24.00%)	<0.01

Proportion of conception per patient in Group A (44.00%) was significantly higher than that of Group B (24.00 %.) (P<0.01).

Discussion:

Different treatment modalities in the form of medical and surgical treatment have been tried over years for ovulation induction in patients with PCOS infertility. Main cause of PCOS infertility is oligo-ovulation or an-ovulation. The incidence of PCOS is increasing day by day. Many research work is going on for treatment of infertility associated with PCOS. Another associated problem with PCOS is insulin resistance. Many drug trials are done to overcome this factor. The present study was done to see the difference in conception rate, number of follicles, size of follicles and endometrial response in patient with PCOS, when they were treated with two different regimen for ovulation induction. In the present study, all the patients were of primary infertility except one who had one previous abortion. Patients of the two groups were age matched. After comparison with previous studies, age group was almost similar. It was observed that the group A receiving Metformin had more number of follicles than group B who had received NAC. It may be due to the better efficacy and insulin sensitizing property of Metformin than

NAC. The study done by Hatem Goodrazi Mo et al [7], had observed mean number of follicles / cycle as 4.3 ± 0.6 in patient treated with Metformin, 2.3 ± 0.3 in patients treated with NAC³. Size of the follicles was measured by ultrasound on day 12 of every cycle in both the groups. Mean + SD of Group A was significantly higher than that of Group B. T. nestler et al.[8] showed that size of follicles >18 mm were significantly higher in group A receiving CC+ Metformin as compared to group B receiving CC+ NAC [9]. All the following outcome signifies that quality as well as quantity of follicles is more and better in Group A than Group B (Goodman & Gilman's 12th) [5]. In this study Endometrium was also statistically thicker in group A than group B because of more growth and mature follicle and higher level of estrogen in group A.

Conception/cycle of Group A was significantly higher than that of Group B.

Badawy A et al (2007) [9], observed in their study significantly higher rate of conception in group treated with CC+ Metformin (15.16%) than in group treated with CC+NAC (4.94%) [10].

Conclusion:

In our study we compared the two Groups, Group A(Clomiphene Citrate+ Metformin) and Group B(Clomiphene Citrate + N-acetyl cysteine) with PCOS infertility, for ovulation induction, their follicular and endometrial response, rate of conception after giving Clomiphene Citrate + Metformin to group A and Clomiphene Citrate + NAC in group B. We found that, number of follicle, size of follicle, Endometrial thickness and rate of conception was better in group treated with CC+ Metformin as compared to group treated with CC+ NAC.

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