Original Article

Comparison of efficacy of clomiphene citrate alone and with metformin for treatment of infertility in polycystic ovarian syndrome

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Objective: To compare the efficacy of clomiphene citrate alone and with metformin for the treatment of infertility in known cases of polycystic ovarian syndrome (PCOS).

Methodology: It was a randomized controlled trial conducted at department of Gynecology and Obstetrics, Cantonment General Hospital, Rawalpindi, Pakistan from July 2015 to December 2015. Total of 128 patients were selected and divided into two groups, each with 64 patients. The inclusion criteria were age between 20-35 years and duration of infertility three years or less, patients who were already diagnosed as case of PCOS. Group A, was offered Clomiphene Citrate alone and Group B was offered Clomiphene Citrate in combination with Metformin for ovulation induction. We gave ovulation induction in both groups for three consecutive cycles. Conception results were compared in both groups. Conception was confirmed by urine for pregnancy test and pelvic ultrasonography.

Results: The mean age of group A was 28.67±2.67 years and mean age of group B was 28.55±2.39 years, both range from 24 to 34 years (P>0.05) which is almost equal in both groups. The mean duration of marriage in Group A was 3.89±1.89 years (range 2 to 8) and mean duration of marriage in Group B was 3.19±1.837 years, (range 1 to 8). In Group A after three cycles total number of patients conceived were10 and in group B, 23 patients had conceived.

Conclusions: Number of patients who conceived with combination of drugs is more because of decreasing insulin resistance but in comparison to clomiphene alone it is not statistically significant. Hence, proving that combination of Clomiphene and Metformin is not better than Clomiphene alone. (Rawal Med J 201;43:285-288).

Keywords: Ovulation induction, conception, PCOS.

INTRODUCTION

Anovulatory infertility comprises about one quarter of patients attending infertility clinic. The polycystic ovarian syndrome (PCOS) is the commonest endocrine disturbance leading to anovulatory infertility and oligomenorrhoea.[1] PCOS is characterized by the presence of enlarged ovaries with multiple small cysts (2-8 mm dia) and hypervascularized androgen secreting stroma.[2] The disease is manifested clinically by signs of androgen excess including hirsutism, alopecia, obesity and menstrual cycle disturbance either oligomenorrhoea or amenorrhoea. Normal ovulatory mechanism which includes development of an ovarian follicle which grows in response to appropriate secretion of FSH becomes dominant and ovulates, gets disturbed in women with PCOS due to androgen excess[3] and hyperestrogenism. Ovarian overproduction of androgens is due to hyperinsulinism and raised insulin levels are recognized as an important feature of PCOS. Insulin lowering therapies such as metformin can bring improvement in insulin resistance and ovarian hyperandrogenism.[4]

Ovulatory response to clomiphene, an effective drug for ovulation induction,[5] can be increased in PCOS by decreasing insulin resistance with metformin. Young females, especially those with obesity and family history of diabetes are presenting with PCOs. High caloric diets and sedentary life style of young generation have contributed towards exaggeration of this multi-system metabolic disorder. The aim of this study was to have an effective ovulation induction regimen.

METHODOLOGY

The study was conducted in the Department of

Obstetrics and Gynaecology, Cantonment General Hospital Rawalpindi from July 2015 to December 2015, using consecutive non-probability sampling. Inclusion criteria were diagnosed cases of PCOS, duration of infertility three years or less and age between 20 to 35 years. Exclusion criteria were any comorbid medical condition, those not living with husband or taking oral contraceptives. A total of 128 patients were selected and divided into two groups. Group A, with 64 patients receiving clomiphene citrate and Group B, with 64 patients receiving clomiphene citrate and metformin. An informed consent was taken from all patients.

Tablet clomid (clomiphene citrate) was given in dose of 50mg, 100mg, and 150mg for three consecutive menstrual cycles in both groups for 5 days starting from 2nd day of menstrual cycle. Tablet glucophage (metformin) was given in dose of 500mg three times a day throughout the menstrual cycle in group B only. Conception rate was assessed for three consecutive menstrual cycles by urine pregnancy test and was confirmed on ultrasonography.

Chi square test was used to compare frequency of conception in 1st, 2nd and 3rd cycles (qualitative) between two groups and data was analysed by using SPSS Version 10. P<0.05 was taken as significant.

RESULTS

The study included 128 patients of COS. The mean age was almost same in both groups and there was no significant difference in age of patients in Group A and Group B (28.67±2.67 vs 28,55±2.39; P>0.05). The mean duration of marriage in Group A was 3.89±1.89 years (range 2 to 8) and mean duration of marriage in Group B was 3.19±1.837 years, (range 1 to 8). The duration of marriage was significantly (P<0.05) higher in Group A as compared in Group B. Rate of primary infertility was less in group A in which 39(60.93%) out of 64 women presented with primary infertility as compared with Group B in which 44(68.75%) out of 64 presented with primary infertility while rate of secondary infertility in Group A was 25 (39.06%) out of 64 women as compared to Group B in which 20(31.25%) out of 64 had secondary infertility (P=0.355).

Table. Comparison of different variables in both groups.

Rate of conception per cycle	Group A	Group B	P- value
1st cycle of conception	2(33.3%)	4(66.7%)	0.403
2nd cycle of conception	3(30%)	7(70%)	0.188
3rd cycle of conception	5(29.4%)	12(70.6%)	0.068

In first cycle of treatment, 2 patients conceived out of 64 patients in Group A, and 4 patients conceived out of 64 in Group B, which shows no significant difference (P=0.403.) between rate of conception between two groups. In second cycle of treatment, 3 patients conceived out of 64 in Group A, and 7 patients conceived out of 64 patients in Group B, which also shows no significant difference (P=0.188.) between rate of conception between two groups. In third cycle of treatment, 5 patients conceived out of 64 patients in Group A, and 12 patients conceived out of 64 patients in Group B, which also shows no significant difference (P=0.068) (Table).

DISCUSSION

Different regimens for ovulation induction in PCOS have been in used like clomiphene citrate, gonadotropins, aromatase inhibitors and metformin. Clomiphene is considered as first line of treatment for anovulatory infertility, when other causes of infertility has been ruled out. On the basis of this theory, clomiphene was given in increasing dose and its effect in the form of conception was noted. Hence proved that with increased dose more patients conceive, showing cumulative effect of clomiphene.

Under the effect of clomiphene more and more follicles are grown resulting in development of more than one mature follicle and increasing chances of pregnancy to occur. This effect may also result in fertilization of more than one mature follicle and possibility of multiple pregnancy. In this study, minor side effects of clomiphene and glucophage were observed in almost two third of patients and no severe side effect like ovarian hyperstimulation syndrome was noted. Palomba et al concluded that there is no difference between clomiphene alone and in combination with metformin as far as fertility is concerned.[6] On the contrary, a study by Moll from Amsterdam showed that addition of metformin to

clomiphene was helpful in treating the patients of PCOS, who are overweight and aged.[7] Same was reported by Zain et al from Malysisia.[8] Our study showed similar results.

A local study by Ayesha had 100 patients and showed rate of ovulation in the group receiving clomiphene alone to be 36% and out of this 44% (almost less than half who ovulated) had conceived while in other group receiving combination of both drugs rate of ovulation was 68% and out of them 52.9% (more than half women ovulated) had conceived.[9] In our study, total number of patients who conceived with clomiphene alone is 15.62% and in those receiving combination drugs, rate of conception was 35.93%. This difference is not statistically significant. Hence, above mentioned study is contradicting with our results. We have only studied for rate of conception and not calculated the rate of ovulation, which can be an important difference in both studies affecting the results.

Another study from Tunis studied 126 patients and ovulatory rate came out to be 32.25% in clomiphene group and 53.12% in group receiving clomiphene with metformin which is statistically significant and also ongoing pregnancies' in both groups have marked difference, proving metformin to be a good addition to clomiphene for ovulation induction.[10] These results are different than our study. This may be because they gave high doses of both drugs (metformin 850mg twice a day and 100mg persistent dose of clomiphene, in every cycle) whereas we gave increasing dose of clomiphene in three cycles starting from 50mg in first cycle to 150mg in third cycle and 500mg persistant dose of metformin thrice a day for all cycles.

A study from Istanbul showed similar pregnancy rates in both groups.[11] Another study from India showed conception rate was 8% with clomiphene alone and 24% with metformin and clomiphene showing statistically significant results.[12] This study contradicts our results as number of patients conceiving on combination of drugs is more but no significant difference from other group as in Indian study.

As in our study, outcome measured was only rate of conception and not the rate of ovulation, which was if measured, result would have been more precise and elaborative showing detailed efficacy of both drugs. Secondly, weight of patients included in study was not considered. It is an important parameter, which affects the rate of ovulation and conception and needs to be considered to develop a relationship between BMI and ovulatory functions.

CONCLUSION

Rate of conception was slightly higher but not statistically significant, when combination of clomiphene and metformin was used for ovulation induction. The difference is not that obvious and had inconclusive results and requires consideration of other parameters like weight and rate of ovulation to reach a more precise and definitive conclusion. Hence our study negates the hypothesis that combination of both drugs is effective for ovulation induction than clomiphene alone.

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