Original Article

Comparative Study of Metformin Versus Clomiphine Citrate for Ovulation Induction in Polycystic Ovary Syndrome at Lady Willingdon Hospital Lahore

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Abstract

Background: Metformin has given quite encouraging results in a number of patients improving overall ovarian health and inducing pregnancies.

Objective: The Purpose of this study was to compare the effectiveness of combined treatment regimen Metformin and Clomiphene citrate with Clomiphene citrate alone for ovulation induction.

Methodology: This randomized controlled trial was conducted over a period of 2 years from Jan. 2008 to Jan 2010. This study includes prospective analysis of PCOS subjects, who were treated in Gynaecological unit II of Lady Willingdon Hospital Lahore. Two hundred subjects were recruited and then divided randomly into two groups, A and B. Group A, included one hundred patients (50%) who were treated with clomiphine citrate only while Group B, included one hundred patients who were treated with Metformin and clomiphine citrate both. The collected data was entered into SPSS version 17 and were analysed accordingly applying descriptive statistics e.g. mean, frequency and analytical e.g. t-test and Chi Square.

Results: Mean age at presentation of group-A was 26.52 ± 0.23 which when compared with that of group – B 26.17 ± 0.25 did not differ statistically (P-Value = 0.306 – in significant). Similarly age at menarche of group A (CC) 12.82 ± 0.08 did not show statistical difference when compared with that of group – B (CC + met) 13.04 ± 0.11 (P-Value = 0.123 – insignificant) or > 0.05. As for as duration of infertility was concerned it was 5.28 ± 0.27 yrs for group – A and 4.99 ± 0.20 years, for group – B. Overall, 125 (62.5%) women ovulated, out of which 46 (36.8%) were from Group – A while 79 (63.2) were from Group – B).

Conclusion: Metformin may be a therapeutic option for PCOS based on improvement in laboratory and clinical parameters. Our results also establish guidelines for metformin treatment with special implication on non-obese patients. It should be recommended for being effective as well as ecnomical.

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Introduction

Polycystic Ovarian Syndrome (PCOS) was first ever described as an entity by Dr. Stein in 1935 describing a group of women with excessive hair, obesity and multiple cysts in ovaries.[1] This is one of the most recurring endocrine disorders among women of reproductive age influencing approximately 6% of them.[2] The prevalence for PCOS shows an increased trend in sub continental region, where Kashmiri Women in India having 37.3% and Pakistani women having 20.7% in different studies.[3-5] The most frequent outcome of this disease is hyperandrogenic anovulatory infertility. The archetypal presentation of this disease is via clinical examinations conducted for obesity assessment, androgen excess (acne, hirsutism, oligomenorrhea) and related infertility. Signs and symptoms for this disorder differ with respect to hormonal imbalance, nevertheless about 5 – 10% women demonstrate full – blown syndrome.[6]

Various clinical, ulrtasonographic and biochemical features are associated with this heterogenous syndrome.[7] PCOS is basically a multidimensional disorder that may show its outcome in different spectrums. At one dimension it may present itself with merely polycystic ovaries.[8,9] Whereas on the other dimension it may encompass a number of typical reproductive problems e.g. obesity, hyperandrognism, menstrual cycle disturbance and infertility, that may occur alone or in combination.[9-11] The possible biochemical involvement may be the elevated circulating levels of LH in the blood as compared to FSH, leading to higher androgen levels and insulin resistance, which in turn promotes higher production of insulin for normal glucose metabolism.[12,13]

Metformin has been repeatedly tested for not merely improvement in PCOS but also for other reproductive problems i.e. regularity in menstrual cycles and pregnancy complications.[14] Metformin has given quite encouraging results in a number of results improving overall ovarian health and inducing pregnancies. Batukan et al in his randomized control trial showed that 65.2% patients got pregnant at the end of Metformin plus CC cycle (p-value = 0.0001).[15] Heard et al reported that Metformin induced substantial pregnancy in 69% (20 / 29) women within 6 months of usage[16]. The ovulatory response to clomiphene citrate (CC) can be increased in obese PCOS women when used in conjunction with metformin. A solid body of literature supports the role of Metformin in reducing PCOS related factors including hyperandrogenism, menstrual irregularities, insulin resistance, decreased ovulation rates, and infertility.[17]

Subjects and Methods

Study Design: Randomized controlled trial.
Duration of Study: A causal comparative study was conducted over a period of 2 years from Jan.2008 to Jan 2010.
Setting: This study includes prospective analysis of PCOS subjects, who were treated in Gynaecological unit II of Lady Willingdon Hospital Lahore.
Sample Size: Two hundred recruited subjects were divided randomly into two groups, A and B. Group A, included one hundred patients (50%) who were treated with clomiphene citrate only while Group B, included one hundred patients who were treated with Metformin and clomiphene citrate both.

Sample Selection Criteria

Inclusion Criteria

- The inclusion criteria was objectively chosen and strictly followed.
- It was mandatory for all patients to have normal uterine cavity (Tubal patency was confirmed) and not to have any chronic medical disorder.
- Also, male partners of all patients had normal semen parameters according to WHO Criteria.

Exclusion Criteria

- Patients with abnormal semen reports of the partner, patients with blocked fallopian tubes & Patients with Medical disorders were excluded from the study.

Data Collection Procedure

Data was collected by research proforma after detailed counselling of the patients about the purpose and method of the study and taking written consent.

Statistical Handling

The collected data was entered into SPSS version 11.5 and analysed accordingly. The quantitative variables

like age, duration of infertility, were presented as means and standard deviation. The qualitative variables were presented as frequency in percentages. Quantitative data was compared by independent sample t-test and Chi-square test was applied for qualitative data. P value < 0.5 was considered as significant.

Results

Mean age at presentation of group – A was 26.52 ± 0.23 years which when compared with that of group-B 26.17 ± 0.25 years did not differ statistically (P-value = 0.306 – in significant). Similarly age at menarche of group A (CC) 12.82 ± 0.08 years did not show statistical difference when compared with that of group – B (CC + met) 13.04 ± 0.11 years (P-value = 0.123 – insignificant) or > 0.05. Mean duration of infertility was 5.28 ± 0.27 years for group – A and 4.99 ± 0.20 years, for group – B.

Oligomenorrhoea was seen in 47 patients in group – A (CC) and in 56 patients of group – B (Met – CC). It appeared to be the most common disturbance. Twenty four (24%) patients in group – A, and forty one (41%) in group – B were with regular menstrual cycle. In group – A, 10 patients and in group-B, three patients were with amenorrhoea. Nineteen patients in group – A and none in group – B showed symptom of dysmenorrhoea.

The sign of hirsutism was seen in 62 subjects of group – A (CC) and 69 subjects of group – B (Met – CC). Mean serum FSH level at presentation of female subjects of group – A undergoing treatment with CC was 5.67 ± 0.13 miu/ml and group-B undergoing treatment with Met – CC was 5.84 ± 0.14 miu / ml. Mean serum LH level of group – A and group – B was 11.9558 ± 0.27 and 12.7428 ± 0.41 respectively. Mean serum FSH and LH was same in both study groups. All the patients included in the study were with Primary infertility having duration of infertility three years and more. In the first treatment cycle induced with 50 mg of CC, 28 (14%) of total 200 patients ovulated, out of which 11 (39.3%) were in group A and 17 (60.7%) in group B. In the second treatment cycle induced with100 mg of CC, a total of 42 (21%) ovulated, out of which 12 (28.6%) belonged to group – A and 30 (71.4%) to group – B. The female subjects who underwent third treatment cycle with 150 mg of CC, a total number of 55 (27.5%) ovulated, out of which 23 (41.8%) ovulated in group – A and 32 (58.2%) in group – B. Overall, 125 (62.5%) women ovulated, out of which 46 (36.8%) were from Group – A while 79 (63.2) were from Group – B). Over all comparison of ovulation in group – A (46%) and group – B 79% showed highly significant value (chi square = 23.23; P value = 0.000-highly significant) indicating quite different results among both groups.

Table 1: Descriptive statistics and comparison of age, age of menarche, duration of marriage, infertility, FSH and LH levels.

	A (n = 100)	B (n = 100)	p-value
Age (years)	26.52 ± 2.320	26.17 ± 2.503	0.306 (insignificant)
Age of Menarche (years)	12.82 ± 0.08	13.04 ± 0.11	0.123 (insignificant)
Duration of marriage (years)	4.2350 ± 1.11	3.8630 ± 1.44	0.043 (significant)
FSH (miu/ml)	5.6718 ± 1.32	5.8449 ± 1.41	0.372 (insignificant)
LH (miu/ml)	11.9558 ± 2.79	12.7428 ± 4.17	0.119 (insignificant)

Table 2: Ovulatory Response in Patients of the Study Groups.

Study Groups	Ovulation	No Ovulation	Total
Group – A	46 (46%)	54 (54%)	100 (100%)
Group – B	79 (79%)	21 (21%)	100 (100%)
p-value	0.0000 (significant)		

Discussion

Polycystic Ovarian Syndrome (PCOS) is not merely a common disorder leading to anovulatory infertility but constitutes other long term health hazards too. Other than obesity, atherosclerosis, hypertension and other intrinsically appeared problems, Endometrial Cancer stays

all time risk too[3-9] (role). Metformin has also been documented as one of the beneficial drugs with positive outcomes. This drug has not only proved itself helpful for inducing pregnancy in patients of PCOS but also gives better clinical outcomes of successful retention of pregnancy.[18,19]

In the last decade, a number of studies have been conducted on usage and affectivity of Metformin initiating a debate of varying results. Some of the studies have yet failed to show any positive outcome, though these results may not merely be confined to the drug but the difference of setting and design of each study.[20,21]

Proceeding with this trend, a prospective study was carried out in the department of gynaecology and obstetrics Unit II at Lady Willingdon Hospital Lahore. The main objective was to determine the effect of clomiphene citrate alone and in combination with insulin sensitizing — agent metformin in ovulation induction. The selection of subjects included in the present study was at random in age range of 21 – 30 years. They presented with mean age of 26.52 ± 0.23 years and 26.17 ± 0.25 years in CC only and metformin – CC treated groups respectively. It was seen that ovulation rates were higher in this age group due to active fertility. This is in agreement with reports that young subjects have a higher probability to ovulate and conceive spontaneously and after ovulation induction.[22,23] Age is important factor for the prediction of chances for spontaneous ovulation and conception in untreated normogonadotrophic sub fertile subjects.[24,25] Similar findings have been reported after exogenous ganodotrophin induction of ovulation and in vitro fertilization treatment in which it was observed that those who conceived were younger 27 ± 4 years.[26] All these results are consistent with the present study.

In the present study mean age at menarche was 12.71± 12 years and 12.88 ± 0.1 years in CC only and Met. – CC groups respectively (did not differ statistically). This figure is similar to other studies as the average age of menarche in UK is 13 years and 95% of female population reached it between 11 to 15 years. The mean age of menarche is 13.29 ± 0.02 years with a range of 10 to 16 years in Pakistan.[27,28] Bano found age of menarche in Pakistani women ranged between 12 to 15 years.[29] Duration of infertility was 5.28 ± 0.27 years and 4.99 ± 0.25 years in group A and group B patients respectively which did not show significant difference. Contrarily, Imani found shorter mean duration of infertility in both the groups (the ovulated and non-ovulated).[30] This difference in study might be due to the fact that patients in the West are more aware and therefore present early. So we can say subjects with shorter duration of infertility responded well to ovulation induction protocol. No pharmacological treatments for PCOS today has reported its effect without any limitation or side effect, like oral hormonal contraception does not improve insulin resistance or obesity issues despite of suppressing ovarian activity.[31] Other treatments involving drugs like clomiphene citrate have shown quite disappointing results with low pregnancy rates.[32] Therefore many studies have now started to focus their trial on affectivity of Metformin for ovulation and to find any other positive results on relating features of PCOS.[33-35]

The present study was carried out to evaluate the effect of Metformin in conjunction with CC in ovulation induction of PCOS subjects. The study was carried out on 200 subjects. The number of subjects who ovulated in CC only and Met. – CC treated groups was 46% and 79% respectively. The subjects showed very significantly higher number of ovulation ($p = 0.000$) in case of Met.CC treatment. The findings in the present study are consistent with those of previous studies reporting that administration of Metformin to PCOS women, increased rates of spontaneous ovulation. In compatible to our results, Kocks, who studied 56 patients, showed 77.7% ovulation in Metformin treated patient and 14.2% in placebo groups ($P = 0.001$) while conception was recorded in 11% of metformin treated group vs. no conception in placebo group.[34] Thus Met – CC may be suggested as an effective, ecnomical and safe medicine for ovulation in primary infertile women suffering from PCOS.

Conclusion

Metformin may be a therapeutic option for PCOS based on improvement in laboratory and clinical parameters. Our results also establish guidelines for metformin treatment. Non-obese women demonstrated statistically significant response to the drug at this dosage therefore these patients may be the main target for the therapy. Met – CC combination should be considered as first step in the provision of fertility assistance in the patients as it is less expensive than other methods of fertility assistance.

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