Original Article

Comparison of Efficacy of Clomiphene Citrate Alone and with Glucophage for Treatment of Infertility in Polycystic Ovarian Syndrome

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Abstract

Objective: To compare the efficacy of clomiphene citrate alone and with Glucophage for treatment of infertility in polycystic ovarian syndrome.
Methodology: This randomized control trial was done during six months from May 2019 to November 2019 at the department of gynecology and obstetrics, Bahawal Victoria Hospital, Bahawalpur. All the married infertile women with polycystic ovarian syndrome of >6 months duration, ages 20 to 35, were included and divided into two groups. Clomiphene citrate tablets were given in doses of 50mg, 100mg, and 150mg for three consecutive menstrual cycles in both groups for five days starting from the second day of the menstrual cycle. Metformin tablet was given in dose 500mg three times a day throughout the menstrual cycle in group B only. Efficacy was measured in terms of conception for three consecutive menstrual cycles by a positive urine pregnancy test and was confirmed on ultrasonography. All the data was recorded via a study proforma, and version 26 of SPSS was used for data analysis.
Results: A total of 114 married infertile women were studied. The average age of women in group A was 30.12 ± 4.33 years, and that of women in group B was 30.22 ± 3.55 years. The mean duration since marriage was 4.23 ± 1.42 years, and the average duration of PCOS was 10.31 ± 2.57 months. Overall average of BMI was 29.75 ± 2.65 kg/m2. Efficacy was seen in 35.09% of patients in the clomiphene citrate only group and in 63.16% in the clomiphene citrate plus metformin group (p = 0.003).
Conclusion: Combined clomiphene citrate and metformin therapy was observed to be the more effective in the treatment of infertility in polycystic ovarian syndrome compared to clomiphene citrate alone therapy.
Keywords: polycystic ovarian syndrome, clomiphene citrate, metformin.
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Introduction

Polycystic ovarian syndrome (PCOS) is a prevalent gynecological and endocrine disease that affects 5–10% of reproductive-age females.[1] PCOS is a challenging and persistent condition that has psychological impacts, including heightened anxiety, depression, and decreased quality of life. It also has reproductive symptoms, such as infertility, high levels of androgens, and excess hair growth, as well as metabolic effects, including impaired glucose tolerance, resistance of insulin, increased risk for type 2 diabetes, and adverse cardiovascular consequences. [1,2] Due to menstrual problems, a lack of ovulation, and hyperandrogenism, PCOS is the leading cause of infertility among reproductive age women.[3] IR is the most significant feature of PCOS, affecting 35–80% of those with the condition. If not properly managed, insulin resistance and increased insulin levels can directly contribute to reproductive problems among women having PCOS.[4]

Insulin resistance not only causes hyperandrogenism and other symptoms of PCOS, but it also increases the risk for cardiovascular diseases and diabetes mellitus in those with PCOS.[1,5] Around 5 million females in the US and 105 million women globally are impacted by this.[5] Combination pills consisting of estradiol and progesterone are utilized in the long-term treatment of PCOS. These pills provide protection for the endometrial lining, regulate menstrual cycles, and improve symptoms such as hirsutism and acne by reducing the

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production of androgens from the ovaries.[6] The cause of PCOS is a combination of genetic and environmental factors. Having a family history of PCOS is one such risk factor. The PCOS' diagnosis can be determined by the presence of two of the three criteria: absence of ovulation, high levels of androgens, and ovarian cysts.

Ovarian cysts can be detected using ultrasound. Other conditions that can cause similar symptoms include adrenal gland overgrowth, low thyroid function, and elevated prolactin levels in the blood.[7] For a number of years, clomiphene citrate has been the first medication prescribed to women with anovulatory PCOS in order to induce ovulation.[6] However, metformin seems to be an oral type of medication that is used to treat type 2 DM. Recently, it has been proven to improve ovulatory cycles in women with anovulatory polycystic ovary syndrome. It achieves this by boosting glucose absorption and utilization in the periphery, which in turn decreases IR.

Metformin, a kind of biguanide, has been shown to improve insulin sensitivity in women having PCOS by decreasing the generation of ovarian androgens. It is possible that this will have a direct impact on the growth of the follicles and cause ovulation.[7] In accordance with the findings of a number of studies conducted in the past, the administration of metformin to CC in CC-resistant instances assists in the achievement of ovulation in 68.6 to 77.7% of the cases.[8-10]

In another study, the conceiving rate with clomiphene alone and clomiphene citrate combined with Glucophage was statistically insignificant.[11] As PCOS is the commonest reason of infertility, the best treatment for this is still controversial. However, the present study has been done to compare the effectiveness of clomiphene citrate alone versus clomiphene citrate with Glucophage for infertility treatment among women with PCOS. As routinely clomiphene citrate is used alone in majority of our setups, so my study will provide the local stats of combined clomiphene citrate and Glucophage use in PCOS. This study may be a useful addition to existing literature, and based on the greater effectiveness of the clomiphene citrate and metformin combination, local clinicians can be encouraged for using this combination instead of clomiphene citrate alone, which ultimately improves the patients' psychosocial well-being by raising the fertility rates in such cases.

Methodology

This randomized control trial was done at the Gynecology and Obstetrics department of Bahawal Victoria Hospital in Bahawalpur and was conducted over a period of six months, from May 2019 to November 2019. Sample size calculation (114 =57 cases in each group) was done, with a 5% level of significance, 80% power of the study, and taking the conception rate with clomiphene alone as 15.62% and with combined clomiphene citrate and metformin as 35.93%.[10] This study included all married women with PCOS and infertility lasting more than 6 months, who were between the ages of 20 and 35 years. All the women with hyperprolactinemia (serum prolactin >40 ng/dL), a bicornuate uterus, chronic liver disease, or renal impairment were excluded. Informed verbal consent was obtained from each woman. The selected patients were then divided into two groups (Group A and Group B) using a random lottery method. In Group A, clomiphene citrate (tablet) was given at doses of 50mg, 100mg, and 150mg for three consecutive menstrual cycles. The medication was taken for 5 days, starting from the second day of the menstrual cycle. This regimen was applied to both groups. However, the drug (metformin) was administered 3 times a day with a dosage of 500mg during the entire menstrual period only in group B. All patients in both groups were evaluated by the researcher herself, and efficacy (measured in terms of conception for three consecutive menstrual cycles by a positive urine pregnancy test and confirmed on ultrasonography) was recorded. All the information (age, BMI, duration of PCOS, duration of marriage, and drug effeteness) was collected on the Performa. The analysis of the data was performed using SPSS version 26.

Results

The age range of the study subjects was 20 to 35 years, with a mean age of 30.22 ± 3.55 years; particularly, the average age of women in group A was 30.12 ± 4.33 years, and in group B it was 29.54 ± 4.76 years. Overall mean duration of PCOS was 10.31 ± 2.57 months, mean duration since marriage was 4.23 ± 1.42 years and average BMI was 29.75 ± 2.65 kg/m^2. Table I

Efficacy was found to be significantly higher (63.16% in group B (clomiphene citrate plus Glucophage]) compared to group A (clomiphene citrate only] (p = 0.003). Table II

As per stratification, the efficacy was statistically significant according to the age group of 31–35 years,

Table I: Descriptive statistics of age, marriage and disease duration and BMI (n=114)

Variables	Group A (n=57)	Group B (n=57)	Total (n=114)
Mean age ((years)	30.12 ± 4.33	*30.22 ± 3.55*	30.07 ± 4.66
Mean duration of marriage (years)	4.28 ± 1.32	4.12 ± 1.59	4.31 ± 1.28
Mean duration of PCO (years)	10.19 ± 2.66	10.58 ± 2.53	10.31 ± 2.57
Mean BMI kg/m^2	29.91 ± 2.51	29.53 ± 2.65	29.75 ± 2.65

Table II: Distribution of patients according to efficacy between both Groups (n=114)

Variable		Group A		Group B		p-value
		N	%	N	%	
Efficacy	Yes	20	35.09	36	63.16	0.003
	No	37	64.91	21	26.84	

Table III: Stratification of efficacy with respect to the effect modifiers (n=114)

Variables		Group A Efficacy		Group B Efficacy		P-value
		Yes	No	Yes	No	
Age groups	20-30	10	16	19	13	0.113
	31-35	10	21	17	08	0.008
Duration of PCOS (months)	7-9	09	19	17	07	0.005
	>9	11	18	19	14	0.122
BMI (kg/m^2)	≤30	09	22	19	13	0.015
	>30	11	15	17	08	0.065

duration of disease of 7–9 months, and BMI <30 kg/m^2 (p-<0.05), as shown in the table III

Discussion

Polycystic ovary syndrome (PCOS) is a varied condition affecting 20% of women during reproductive age.[10,12] It is characterized by prolonged anovulation, elevated levels of androgens, and is the most commonly occurring hormonal disorder in women.[10,13] It is a multifaceted condition that has a negative impact on fertility in women throughout the world. However, for obese women with PCOS, losing weight leads to a decrease in insulin and androgen levels, resulting in improved fertility outcomes. Regarding the induction of ovulation among these individuals, clomiphene citrate (CC) was the primary medication, although it continues to have a significant failure rate.

Moreover, those who used Clomiphene citrate for >6 cycles had a greater chance of developing ovarian cancer.[10,14,15] This study was carried out to evaluate the effectiveness of clomiphene citrate by itself as well as in combination with Glucophage in the infertility treatment of patients diagnosed with PCOS, and the efficacy was seen to be higher 63.16% in the clomiphene citrate plus Glucophage group (p = 0.003). Consistently in a study, the Glucophage and clomiphene combination has shown rate of ovulation as 76.2% compared to clomiphene alone as 38.1% along with pregnancy rate 28.6% with CC and 66.6% with metformin and clomiphene citrate.[10] Another study also reported that 15.62% of patients became pregnant using only clomiphene, while in the combined group the conception rate was 35.93%.[11] Similarly, in a randomized clinical trial, it was discovered that the combination of metformin and clomiphene citrate led to a higher frequency of ovulation compared to the group that received clomiphene citrate alone (P = 0.0016), and finally, they observed that the combination treatment should be initiated early in the course of treatment.[16] In the line of this study, Uzma S et al[17] reported that the combination of clomiphene citrate and metformin is significantly more effective in treating infertility in patients with polycystic ovarian syndrome compared to clomiphene citrate alone. Consistently, Lin W et al[18] also observed that the use of clomiphene citrate (CC) combined with metformin (MET) results in a higher clinical pregnancy rate compared to using CC alone, but there is no notable difference in the ovulation rate. However, according to a recent randomized control trial, the results of adding metformin to clomiphene therapy suggest that the addition of metformin does not result in an improvement in ovulation rate compared to using clomiphene alone.[19]

In accordance to a previous local study, involving 100 patients, found that 36% of the patients who received only clomiphene ovulated, and of these, 44% became pregnant. In contrast, 68% of the patients who received both clomiphene and metformin ovulated, and over half of these, 52.9%, became pregnant.[20] In this study, efficacy was significantly higher in obese women. Metformin and thiazolidinediones, are the preferred treatment options for polycystic ovary syndrome (PCOS). These agents have favourable effects on both metabolism and hormones/ovaries, including improved glucose, lipid, and anti-inflammatory profiles, as well as improved reproductive health, restoration of ovulation and menstrual cycles, reduced production of androgens, and increased pregnancy rates.[10] Treatment options for infertility in women with PCOS include lifestyle modifications, such as weight loss and regular exercise, as well as medications such as clomiphene citrate and

metformin. It is important for women with PCOS to seek guidance from a reproductive endocrinologist or infertility specialist to determine the best course of action. Additionally, it is important for women with PCOS to maintain a healthy lifestyle and manage their symptoms, as this can positively impact their fertility outcomes.

Conclusion

The use of clomiphene citrate in combination with metformin was concluded to be a more effective treatment for infertility in women with polycystic ovary syndrome (PCOS) compared to using clomiphene citrate alone. However, the study has some limitations, the most significant of which is its small sample size; therefore, more comprehensive studies are recommended on the subject.

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