DOI: https://doi.org/10.53350/pjmhs2023174606

ORIGINAL ARTICLE

Efficacy of Clomiphene Citrate Alone Versus Clomiphene Citrate Plus Metformin in Anovulatory Infertility in Polycystic Ovarian Syndrome

TANZILA RAFIQ[1], NAHEED HAYAT[2], SADIA ZAINAB[3], SUMAIRA MAQSOOD[4], NAHEED FATIMA[5], PIYA MUHAMMAD MUSAMMAT RAFI[6]
[1,2,3]*Assistant Professor Department of Obstetrics & Gynecology CMH Institute of Medical Sciences, Bahawalpur*
[4]*Senior registrar Department of Obstetrics & Gynecology BVH Bahawalpur*
[5]*Professor Department of Obstetrics & Gynecology CMH Institute of Medical Sciences, Bahawalpur*
[6]*Senior Registrar Department of Ophthalmology Bahawal Victoria Hospital, Bahawalpur*
Correspondence to: Tanzila Rafiq, Email: tanzilarafiq@hotmail.com, Cell: 0300-6891222

ABSTRACT

Objective: To compare the efficacy of clomiphene citrate and clomiphene citrate with metformin in anovulatory infertility with PCOS (polycystic ovarian syndrome (PCOS).

Study Design: Randomized controlled trial.

Place and Duration of Study: This research took place in the Department of Gynecology and Obstetrics at the combined military hospital Bahawalpur. The study was carried out over a six-month period, starting on 1st November 2022 and concluding on 30 April 2023

Materials and Methods: The study comprised 176 married women aged between 18 and 40 years who had been experiencing anovulatory infertility and PCOS for more than 6 months. In group A, for a period of three menstrual cycles, patients received 500 mg of metformin three times a day consistently and 100 mg of clomiphene citrate daily from the fifth to the ninth day of their menstrual cycle. In contrast, patients in group B were given 100 mg of clomiphene citrate daily from the fifth to the ninth day of their menstrual cycle for up to three months. We recorded and analyzed the treatment efficacy for all participants in both groups.

Results: In this study, the metformin and clomiphene combination showed a 71.59% ovulation rate compared to clomiphene alone (39.77 %). The pregnancy rate was 31.82% with clomiphene citrate (CC) and 64.77% with a combination (clomiphene citrate and metformin). Efficacy in the study was observed in 57 (64.77%) patients treated with metformin and CC. group and 28 (31.82%) patients in the clomiphene citrate alone group (p = 0.002).

Conclusion: The findings from this study suggest that the combination of clomiphene citrate and metformin demonstrated superior efficacy compared to the use of clomiphene citrate alone in treating anovulatory infertility associated with polycystic ovary syndrome.

Keywords: Polycystic ovarian syndrome, clomiphene citrate, metformin.

INTRODUCTION

PCOS is a prevalent endocrine/metabolic disorder in women with a disputed definition. defined ovulatory dysfunction consisting of symptoms ranging from clinical or biochemical hyperandrogenism, amenorrhea, and oligomenorrhea. causes hirsutism, acne, alopecia, and oligomenorrhea.[1] Patients with polycystic ovary syndrome exhibit high levels of androgen secretion, leading to overproduction of estrogen precursors within the granulosa cells. Owing to hyperinsulinemia, luteinizing hormone receptors in granulosa cells become active earlier, stimulating aromatase production. As a result, when estrogen production is increased, luteinizing hormone (LH) has positive feedback effects and follicle-stimulating hormone (FSH) has a negative feedback effect, which ultimately disrupts folliculogenesis.[2] Chronic anovulation and subsequent infertility result from hyperandrogenism and insulin resistance.[3]

Approximately 6.5% to 8.0% of women of reproductive age are affected by PCOS, which translates to around in USA about 5 million and globally around 105 million women.[4]

Ovulatory dysfunction, which is responsible for 40% of all cases of female infertility, is often attributable to a common disorder known as Polycystic Ovary Syndrome (PCOS).[5] PCOS is a common endocrine disorder, principally marked by anovulation, irregular menstrual cycles, hyperandrogenism, and the existence of polycystic ovaries. Typically, the diagnosis of PCOS is made based on the identification of polycystic ovaries. It's estimated that this condition could affect as many as 15-20% of women.[6] For women with PCOS who are looking to get pregnant, promoting ovulation is generally viewed as the first line of treatment.[7]

Chronic anovulation and ovarian hyperandrogenism are strongly associated with PCOS and hyperinsulinemia. On the contrary, fertility outcomes can be improved and there can be a reduction in androgen and insulin levels in women with PCOS who go for a weight reduction.[8]

Clomiphene citrate (CC) is typically employed as the initial treatment for inducing ovulation in patients diagnosed with PCOS, but it often results in a high rate of unsuccessful attempts. Extended usage of CC beyond six cycles could elevate the risk of ovarian cancer among these patients. Metformin is known to enhance insulin resistance in women diagnosed with PCOS, subsequently boosting the frequency of ovulation and the likelihood of pregnancy.[10]

Since PCOS is a prevalent cause of anovulatory infertility and the treatment options, there is still no clear consensus, and the purpose of this study was to verify and compare the effectiveness of clomiphene citrate standalone versus combination therapy with clomiphene citrate in + metformin for anovulatory infertility in individuals with PCOS in our local population. Currently, clomiphene citrate is commonly used as a standalone treatment in our medical centers. This study aimed to provide local data on the use of combined (CC)clomiphene citrate and metformin in patients with PCOS. If this combination proves to be more effective, it may encourage clinicians to adopt it as a routine treatment for infertility in patients with PCOS, leading to improved pregnancy rates and enhanced psychosocial well-being.

MATERIAL AND METHODS

The Department of Obstetrics & Gynecology at Combined military Hospital in Bahawalpur conducted a randomized controlled trial from 1st November 2022 to 30 April 2023.

A total of 176 married females along with anovulatory infertility and polycystic ovarian syndrome aged < >6 month of duration and having age 18-40 years were selected.

Patients with hyperprolactinemia, defined as prolactin levels greater than 500Miu/l, and hypothyroidism, defined as TSH levels greater than 5.2 mIU/l and FT3 <1.5pg/ml, FT4<0.8pg/ml, T3<70 ng/dl, T4 <5.2 µg/dl), history of CKD(chronic kidney disease) (s/creatinine mg/dl), previous genital surgery, unwillingness to be included in the study, and lost to follow-up were excluded.

Written and informed consent was taken (written each informed). Two groups were randomly assigned to groups A and B.

In Group A, participants were administered a consistent dose of metformin, specifically 500 mg three times a day starting from the first cycle and continuing for three months. In addition, they

received 100 mg of clomiphene citrate daily from the 5th to the 9th day of their menstrual cycle. On the other hand, participants in Group B were given 100 mg of clomiphene citrate daily from the 5th to the 9th day of their menstrual cycle, and this regimen was followed for up to three menstrual cycles. The effectiveness of the treatments was evaluated for all the participants in both groups, following the set operational definition, and all results were recorded. Other details like age, Body Mass Index (BMI), duration of PCOS, Diabetes Mellitus (DM), and smoking habits were also documented using a standardized form.

All data were processed and examined using the SPSS software, version 20.0. Factors such as age, length of marriage, duration of PCOS, height, weight, and BMI are expressed as averages along with their standard deviations. Other variables like the presence of diabetes mellitus (yes/no), smoking habits (yes/no), occurrence of ovulation (yes/no), pregnancy rate (yes/no), and treatment efficacy (yes/no) are expressed in terms of frequencies and percentages. The chi-square test was utilized to compare efficacy between the groups, and any p-value less than 0.05 was deemed to denote statistical significance.

RESULTS

The participants' ages in this study ranged from 16 to 40 years, with an average age of 29.82 ± 4.64 years. The average age for women in Group A was 29.78 ± 4.78 years, while in Group B it was 29.84 ± 4.21 years. The average duration of PCOS was noted to be 10.31 ± 2.57 months. The average period from marriage was 4.23 ± 1.42 years. The average height was 154.43 ±9.29 cm, and the average weight was 82.33 ± 6.87 kg, with a mean BMI of 29.75 ± 2.65 Kg/m².

The purpose of this study was to compare the effectiveness of clomiphene citrate (Group A) and a combination of clomiphene citrate and metformin (Group B) in treating anovulatory infertility among patients diagnosed with polycystic ovarian syndrome (PCOS). Each group consisted of 88 participants.

Table 1 displays the remarkable difference in effectiveness between the two groups. In Group A, a successful outcome was observed in 57 out of 88 patients (64.77%), while only 28 out of 88 patients (31.82%) in Group B displayed a similar outcome. This result was statistically significant with a p-value of 0.0001, suggesting that clomiphene citrate alone had a greater effect than the combined use of clomiphene citrate and metformin in these patients.

The effectiveness was further stratified by various factors, including age (Table 2), duration of PCOS (Table 3), length of marriage (Table 4), and BMI (Table 5). Across all stratifications, clomiphene citrate (Group A) consistently showed superior effectiveness compared to the combination therapy (Group B).

Specifically, as per Table 2, clomiphene citrate (Group A) was significantly more effective for both age groups 16-30 and 31-40 years compared to the combination therapy (Group B), with respective p-values of 0.009 and 0.0001.

Table 3 shows effectiveness stratified based on PCOS duration. For both time ranges (7-9 years, >9 years), clomiphene citrate (Group A) proved to be more effective, yielding p-values of 0.0001 and 0.007, respectively.

As per Table 4, the data is stratified based on the length of marriage. For both periods (<5 and >5 years), Group A was found to be significantly more effective than Group B, with respective p-values of 0.002 and 0.001.

Lastly, Table 5 illustrates effectiveness stratified based on BMI. Again, in both categories (BMI<27 kg/m², BMI>27 kg/m²), clomiphene citrate (Group A) was significantly more effective than combination therapy (Group B), with p-values of 0.002 and 0.001, respectively.

In conclusion, our study suggests that clomiphene citrate alone (Group A) has a considerably greater effectiveness than when it is combined with metformin (Group B) in treating anovulatory infertility in patients with PCOS. This result holds true irrespective of factors such as age, duration of PCOS, length of marriage, and BMI.

Table-1: Distribution of patients according to efficacy between both Groups

		Group A(n=88)		Group B (n=88)	
		No.	%	No	%
Efficacy	Yes	57	64.77	28	31.82
	No	31	35.23	60	68.18

P-value=0.0001

Table-2: Stratification of efficacy with respect to age group.

Age of Patients (Years)	Group A(n=88)		Group B (n=88}		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
16-30	30	18	15	28	0.009
31-40	27	13	13	32	0.0001

Table-3: Stratification of efficacy with respect to PCOS duration.

Duration of PCOS (Years)	Group A(n=88)		Group B (n=88)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
7-9	28	14	11	29	0.0001
>9	29	17	17	31	0.007

Table-4: Stratification of efficacy with respect to duration of marriage.

Durations of Marriage (Years)	Group A(n=88)		Group B (n=88)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
<5	40	26	23	45	0.002
>5	17	05	05	15	0.001

Table-5: Stratification of efficacy with respect to BMI.

BMI (kg/m²)	Group A(n=88)		Group B (n=88)		p-value
	Efficacy		Efficacy		
	Yes	No	Yes	No	
<27	14	06	05	17	0.002
>27	43	25	23	43	0.001

In our discussion, we evaluated the efficacy of clomiphene citrate as a standalone treatment in comparison to a combined regimen of clomiphene citrate and metformin for the management of anovulatory infertility in patients diagnosed with PCOS. It was observed that the group who were administered both metformin and clomiphene displayed a higher rate of ovulation (71.59%) and a higher incidence of pregnancy (64.77%). These figures were significantly greater than those seen in the group that received only clomiphene, where the ovulation rate stood at 39.77%, and the pregnancy rate was 31.82%. This observed difference between the two groups was statistically significant, with a p-value of 0.002.

In a Jordanian study comparing (CC)clomiphene citrate-resistant women with PCOS to placebo-CC controls, it was discovered that metformin and clomiphene citrate (CC) increased ovulation (68.6% vs. 25%, p = 0.05) and pregnancy rates (56.3% vs. 16.6%, p 0.005). However, ovarian hyperstimulation was also observed in the latter group. Similarly, a controlled experiment conducted in India revealed that the combination of metformin and CC increased pregnancy rates (24% versus 8% with CC alone) and ovulation rates (p=0.0016) without increasing the risk of hyperstimulation. In contrast, 24% had nausea and vomiting and 80% reported appetite reduction. This combo medication should be started as soon as possible, according to the study's findings.[11]

Vandermolen et al. conducted a randomized, placebo-controlled, double-blind study to determine whether metformin, when used in conjunction with CC, can boost ovulation and pregnancy rates (PCOS diagnosed women) there was drug resistant on with PCOS. The metformin plus CC group had higher rates of conception (55% vs. 7) and ovulation (75% vs. 27%) than the control group.[12] Zain et al. investigated the effectiveness of metformin, CC, and metformin with CC in patients with PCOS. They discovered that the metformin + CC group had the highest success rates for both conception (21.1%) and ovulation (68.7%).

The authors concluded that CC should be the first-line treatment for these patients.[13]

In contrast to Zain et al. 's study, Neveu et al. observed comparable ovulation and conception rates in patients treated with standalone metformin therapy or with (CC) clomiphene citrate +metformin. They recommend metformin since it is safe and efficient regardless of weight or insulin levels for PCOS patients ovulation induction.[14]

For females diagnosed with PCOS who do not respond to clomiphene citrate, the inclusion of metformin in their therapeutic regimen has demonstrated positive outcomes in terms of enhancing ovulation, achieving pregnancy, and resulting in live births. The combination of clomiphene citrate and metformin has been found to bolster the rates of ovulation and pregnancy among PCOS patients who have obesity. However, it's notable that this combination therapy does not appear to significantly influence the rate of live births.[15-16] According to the guidelines for managing infertility in PCOS, it is suggested that the combined treatment of metformin and clomiphene citrate should be considered for women diagnosed with PCOS who are either resistant to clomiphene citrate and/or are obese. This combination therapy has been recommended for the improvement of patient outcomes.[17-19]

The research by Abu Hashim and colleagues indicated that women with PCOS who are resistant to Clomiphene citrate and subsequently administered a combination of metformin and clomiphene citrate have a reduced probability of ovulation and pregnancy compared to those treated with gonadotrophins alone. This was represented by an odds ratio of 0.25 (95% CI, 0.15—0.41; across 3 RCTs with 323 women) and an odds ratio of 0.33 (95% CI, 0.13-0.85; across 2 RCTs with 170 women).[20] A randomized controlled experiment was conducted on 42 women with PCOS at a hospital in Saudi Arabia. Half of the women received CC plus metformin, whereas the other half received CC alone. The rates of regular cycles (71.4%), ovulation success (76.2%), and pregnancy (66.6%) were all higher in the metformin-treated patients than in the only (CC) clomiphene citrate-treated patients (38.1%). Throughout research, participants in both groups were given escalating doses of CC.[21]

CONCLUSION

This study concluded that the effectiveness of combined clomiphene citrate and metformin therapy is higher than that of clomiphene citrate standalone therapy in anovulatory infertility with polycystic ovarian syndrome. Therefore, we recommend that first-line combined therapy of (clomiphene citrate and metformin) should be used as first-line therapy for infertility in (PCOS)polycystic ovarian syndrome that leads to a surge in the rates of pregnancy in these specific patients, thus improving the psychological and social life of the patients in care.

REFERENCES

1. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013;98:4565-92.
2. Vause TD,Cheung AP, Sierra S, Claman P,Graham J, Guillemin JA, et al. Ovulation induction in polycystic ovary syndrome. J Obstet Gynaecol Can. 2010;32(5):495-502.
3. Begum Mr, Fedrous J, Begum A, Quadir E. Comparison of efficacy of aromarase inhibitor and clomiphene citrare in induction of ovulation in polycystic ovarian syndrome. Fertil Steril. 2009;92(3):853-57.
4. Susan MS, Kristen AP. Epidemiology diagnosis and management of polycystic ovary syndrome. Clin Epidemiol. 2014;6:1-13.
5. Kamath infertility: Adebate. Reprod Biol Emdocrinol. 2011;9:86.
6. Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol. 2013;6:1-13.
7. Bajelica A, Trninic-pjevic A, Mladenovic-Segedi L, Cetkovic N, Petrovic D. Comparison of the efficiency of clomiphene citrate and letrozole in combination with metformin in moderately obese clomiphene citrate-resistant polycystic ovarian syndrome patients. Srp Arh Celok Lek. 2016;144(3-4):146-50.
8. Messinis IE, Messinis CI, Anifandis G, Dafopoulos K. Polycystic ovaries and obesity. Best Pract Res Clin Obstet Gynaecol. 2014;29(4):479-88.
9. Angel M, Ghose S, Gowda M. A randomized trial comparing the ovulation induction efficacy of colmiphebe citrate and letrozole. J Nat Sci Biol MED. 2014;5(2):450-52.
10. Tso LO, Costello MF, Albuquerque LE, Andriolo RB, Macedo CR. Metformin treatment befor and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2014;18:1.
11. Dasari P, Pranahita GK. The efficacy of metformin and clomiphene citrate combination compared with clomiphene citrate alone for ovulation induction in infertile patients with PCOS. J Hum Reprod Sci. 2009;2:18-22.
12. Maria JI, Nestler JE. Insulin-lowing drugs in polycystic ovary syndrome. Obstet Gynecol Clin North Am. 2001;153-64.
13. Zain MM, Jamaluddin R, Ibrahim A, Norman RJ. Comparison of clomiphene citrate, metformin, or the combination of both for first-line ovulation induction, achievement of pregnancy, and live birth in Asian women with polycystic ovary syndrome: A randomized controlled trial. Fertil Steril. 2009;91:514-21.
14. Neveu N, Grangern L, St-Michel P, Lavoie HB. Comparison of clomiphene citrate, Metformin, or the combination of both for first-line ovulation induction and achievement of pregnancy in 154 women with polycystic ovary syndrome. Fertil Steril. 2007;87:113-20.
15. Costello MF, Misso ML, wong J, Hart R, Rombauts L, Melder A et al. The trearment of infertility in polycystic ovary syndrome: a brief update. Aust N Z J Obstet Gynaecol. 2012;52:400-3.
16. Misso ML, Teede HJ, Hart R, Wong J, Rombauts L, Melder AM, et al. Status of clomiphene citrate and metformin for infertility in PCOS. Trends Endocrinol Metab. 2012;23:533-543.
17. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013;98:4565-92.
18. Goodman NF, Conin RH, Futterweit W, Glueck JS, Legro RS, Carmina E. American Association of Clinical Endocrinologists (AACE); American College of Endocrinology (ACE); Androgen Excess and PCOS Society. American Association of Clinical Endocrinologists, American College of endocrinology, and Androgen Excess and PCOS Society Disease State Clinical Review: Guide to The Best Practices in the Evaluation and Treatment of Polycystic Ovary Syndrome – part2. Endocr pract. 2015;21:1415-1426.
19. Balen AH, Morley LC, Misso M, Franks S, Legro RS, Wijeyaratne CN,et al. The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. Hum Reprod Update. 2016;22:687-708.
20. Abu Hashim H, Foda O, Ghayaty E. Combined metformin clomiphene in clomiphene citrate alone: Polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trias. Acta Obstet Gynecol Scand. 2015; 94:921-930.
21. Ayaz A, Alwan Y, Farooq MU. Metformin_____clomiphene citrate vs. clomiphene citrate alone: Polycystic ovarian syndrome. L. Hum Reprod Sci. 2013;6(1):15-8.