



ORIGINAL ARTICLE

Efficacy of clomiphene citrate alone compared with combination of clomiphene citrate and metformin for treatment of infertility in polycystic ovarian syndrome (PCOS).

Syeda Uzma¹, Adiba Akhtar Khalil², Rabiya Akbar³, Tallat Shaheen⁴

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ABSTRACT... Objective: To evaluate the efficacy of clomiphene citrate compared with clomiphene citrate and metformin combination used as infertility treatment in polycystic ovarian syndrome. **Study Design:** Randomized Controlled study. **Setting:** Combined Military Hospital, Nowshera, KPK. **Period:** March 2021 to November 2021. **Materia & Methods:** One hundred and forty eight infertile patients aged between 20 to 34 years diagnosed with PCOS were enrolled for the investigation. Using blocked randomization technique, the participants were divided into two groups. Group A patients received clomiphene citrate 50 mg day on days 2 to 6 and dose was gradually increased to 150 mg day. Patients in Group B received metformin 500 mg three times a day along with the above mentioned dosage of clomiphene citrate. Collectively, the patients in both groups were provided with a follow up for six months. Efficacy in both groups was assessed on the basis of positive urine pregnancy test. **Results:** The rate of ovulation in group B was high in comparison to group A (39.2% vs 21.6%; P value = 0.02) the results were statistically significant. The rate of efficacy/conception in group B was significantly greater as compared to group A (32.4% vs 16.2%; P value = 0.02). **Conclusion:** We conclude that clomiphene citrate along with metformin, used in combination is significantly much efficacious as compared to clomiphene citrate alone for treating infertility in patients with polycystic ovarian syndrome.

Key words: Clomiphene, Metformin, Polycystic Ovarian Syndrome.

INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a condition in which the production of an abnormal volume of androgen, their regular menstrual cycle takes place. Multiple small liquid-containing sacs are formed in the ovaries.¹ PCOS is a diverse condition with its adverse effect related to infertility in women is recorded 38.5% among women in their reproductive age around the world.² Pakistan is listed among the highly populated countries around the globe with an increasing rate of the population nearly 2% infertility rate of (21.9%). In Pakistan recorded prevalence of infertility is 21.9%.³

Studies suggested that women affected with PCOS have shown that it is the most prevalent

endocrine irregularity among women in their reproductive age.⁴ Patients clinically diagnosed with PCOS are commonly manifested with signs and symptoms including hirsutism, alopecia, disturbed menstrual cycle (oligomenorrhoea or amenorrhoea), obesity, and infertility. In addition, patients with PCOS are usually observed with a higher risk of heart disease, type II diabetes, and endometrial cancer.^{5,6}

Approximately one-quarter of women visiting infertility treatment centers are associated with anovulatory infertility. Experts consider PCOS as most common endocrine disorders often leading to oligomenorrhoea and anovulatory infertility.⁷ Moreover, reports suggested that numerous small ovarian cysts are usually observed in

1. FCPS, Consultant Obs & Gynae, Combined Military Hospital, Nowshera.
2. FCPS, Consultant Obs & Gynae, Associate Professor, Combined Military Hospital, Risalpur.
3. FCPS, Consultant Obs & Gynae, Combined Military Hospital, Nowshera.
4. FCPS, Consultant Obs & Gynae, Associate Professor, United Medical Complex, Rawalpindi.

Correspondence Address:
Dr. Adiba Akhtar Khalil
Department of Obs & Gynae,
Combined Military Hospital, Risalpur.
dradibaakhtar@gmail.com

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PCOS.⁸ Due to the excess of androgen and hyperestrogenism usual ovulatory process that involves the growth of an ovarian follicle, develops as a result of proper FSH production becomes paramount and ovulation occurs, affected in women with PCOS.⁹ The prominent etiology for ovarian excessive production of androgens is hyperinsulinism or increased level of insulin which is also identified as PCOS key attribute.¹⁰

Metformin for non-obese women is an effective therapeutic ovulation induction agent in the treatment of anovulatory infertility, which also helps in lowering the Insulin level and has also shown promising results regarding ovarian hyperandrogenism and insulin resistance.¹¹ Clomiphene is also considered an effective therapeutic choice in the treatment of anovulatory infertility with a high conceiving rate, this treatment is categorized with a modest administration, low cost, and minimum side effects.¹² Diabetes mellitus (DM) and obesity play a vital role in the development of PCOS among adult females. Unhealthy dietary habits such as high caloric diets and lack of exercise reflect a different type of multi-system metabolic disorder among the young population. The study aims to evaluate the effective ovulation induction therapy.

MATERIAL & METHODS

The following investigation was carried out at (Combined Military Hospital, Nowshera, KP) from March 2021 to November 2021. The study was approved by ethics committee of the institute (REF/11/21). The study included 148 infertile participants aged between 20 to 34 years diagnosed with PCOS. The sample was calculated using openepi web-based sample size calculator taking estimated frequency of Clomiphene citrate alone 12.16% and combination of Metformin and Clomiphene citrate 31.08%¹³, margin of error 5% and confidence interval 95%. History was taken from all patients. The physical examination was performed on all patients and transvaginal ultrasound done to confirm PCOS and exclude confounders from study.

The participants include in the study using

blocked randomization technique, the patients were divided into two groups. Group A patients received 50 mg/day of clomiphene citrate on 2nd and 6th day, and dose increased gradually to 150 mg/day. Patients in Group B received metformin 500 mg three times a day along with the above mentioned dosage of clomiphene citrate. Among the total participants, all participants went through a followup for the period of six months. The patients were advised to have unprotected intercourse at least two to three times a week after menstruation. The patients participated in this study were provided a follow up for six menstrual cycles for ovulation confirmed on ultrasonography. Urine pregnancy test was done for confirmation of pregnancy. Efficacy in both groups was assessed on the basis of positive urine test for confirmation of conception.

Data was analyzed using IBM SPSS 20, calculating the frequencies and percentages as the categorical variables analysis whereas mean and standard deviation was applied for the numerical variables. Pearson's chi square test was utilized to estimate the efficacy between the two groups while considering a p value less than 0.05 to be significant.

RESULTS

The following investigation included 148 PCOS patients. The mean age of the participants in group A was 27.66 ± 4.61 years and in group B it was 27.45 ± 4.14 years. No statistical significance was observed for the means of ages of participants in both groups ($P > 0.05$). Means of the duration of infertility in both groups were determined and found to be 4.19 ± 2.39 years in group A and 4.84 ± 2.08 years in group B with no statistical significance between both groups ($P > 0.05$). Table 1 reflects the comparison of ovulation between both groups. The rate of ovulation in group B was found to be higher as compared to group A (39.2% vs 21.6%; P value = 0.02) the results were statistically significant. Table 2 reflects the comparison of efficacy between both groups, the rate of efficacy was higher in group B in comparison with group A (32.4% vs 16.2%; P value = 0.02), group B had suggestively higher efficacy rate as compared to group A.

		Group A (Clomiphene Citrate Alone)	Group B (Metformine+ Clomiphene Citrate)		
Ovulation	Yes	16 (21.6%)	29 (39.2%)	45 (30.4%)	0.02
	No	58 (78.4%)	45 (60.8%)	103 (69.6%)	
Total		74 (100.0%)	74 (100.0%)	148 100.0%	

Table-I. Comparison of ovulation between groups

		Group A (Clomiphene Citrate Alone)	Group B (Metformine+ Clomiphene Citrate)		
Efficacy	Yes	12 (16.2%)	24 (32.4%)	36 (24.3%)	0.02
	No	62 (83.8%)	50 (67.6%)	112 (75.7%)	
Total		74 (100.0%)	74 (100.0%)	148 100.0%	

Table-II. Comparison of efficacy between groups

DISCUSSION

The inability of women aging below 35 to conceive following an year of regular sexual intercourse with no use of contraception is termed as infertility. This duration may be shortened to 6 months in women over 35 years of age.¹⁴ Epidemiological data show that around 10 to 15% of all couples have difficulty getting pregnant (primary infertility). The most common determinant of female infertility, contributing nearly 25% was ovulatory disorder. Among the women with infertility, an association of PCOS have been observed with approximately 75% of women who are infertile due to anovulation. Generally, clomiphene citrate has been reported as the first line of treatment for the induction of ovulation in PCOS affected females.¹⁵ It has also been reported that a variable proportion of women who survive polycystic ovarian syndrome will neither ovulate nor become pregnant even after the treatment with clomiphene citrate. In fact, after treatment with clomiphene citrate, the ovulation rate is around 70-80% with a pregnancy rate of around 40%.^{16,17}

The data on the use of metformin + clomiphene on induction of pregnancy and rate of delivery in women with PCOS is scarce. In one trial, 33.1% of women with obesity having primary infertility in the group with combination drugs whereas in the group that was given clomiphene citrate alone, 30.6 percent were pregnant.¹⁸ It has been reported in another trial that in women treated with a combination of metformin and clomiphene, the pregnancy rate was observed to be 55%,

compared to clomiphene given in combination with placebo (7%).¹⁹ In 3 randomized clinical trials¹⁹, clomiphene and metformin given in combination out performed in inducing ovulation in women with PCOS as compared to treatment with clomiphene only. In our study, combination therapy was significantly ($P = 0.02$) more effective (32.4%) as compared to monotherapy by clomiphene (16.2%).

A study conducted by Wang R. et al²⁰, evaluated the effects of clomiphene alone and clomiphene and metformin given in combination. The study resulted in a higher pregnancy rates, which is consistent with the findings of our study. The efficacy was observed to be best for Letrozole (81%) in terms of live births, whereas that by follicle stimulating hormone was 74 %. Clomiphene and metformin given in combination presented 71% efficacy, while tamoxifen, clomiphene and metformin demonstrated 48, 36 and 30% efficacy, respectively. The lowest frequency was seen in placebo or no treatment which was found to be 10 %.²⁰

In a local study conducted by Ambreen Fatima²¹, 15.62% patients conceived with clomiphene alone, while the rate of conception in those taking combination medications was 35.93%. The results were comparable to our results.

As compared to clomiphene citrate or metformin alone, the combination of both presented a higher pregnancy rate. On comparison of clomiphene

citrate monotherapy with a combination therapy by clomiphene citrate and metformin, the odds ratio for pregnancy is 1.8 (1.35– 2.42), which suggested that using both drugs in combination have shown better treatment along with 1.8 times more chances of pregnancy as compared to the individual drugs²², further supporting our findings.

In another study, Airao BB et al²³ discovered that the ovulatory rate with metformin plus clomiphene citrate was greater when associated to clomiphene citrate given as monotherapy in the infertile PCOS patients. In our study the ovulatory rate was 21.6% in clomiphene citrate alone group while the combination group showed a higher rate of 39.2%, which is comparable to the afore mentioned study. When 150 mg of clomiphene citrate and metformin was introduced in the body as a combination for over three cycles, the ovulatory rate increased. Clomiphene citrate and metformin given as a combination therapy showed better pregnancy rates as compared to clomiphene citrate even in patients that had PCOS which is already resistant to the drug clomiphene citrate. As a result, at the early stages of the treatment, the mentioned treatment should be initiated.

CONCLUSION

From our study, we conclude that there was a significantly comparable difference between the efficacies of treatments provided by clomiphene citrate monotherapy and a combination of clomiphene citrate along with metformin treating infertile women with the PCOS. Therefore we recommend the combination therapy for treatment of infertile patients of PCOS.




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REFERENCES

1. Kolesnikova LI, Kolesnikov SI, Darenskaya MA, Grebenkina LA, Nikitina OA, Lazareva LM, Suturina LV, Danusevich IN, Druzhinina EB, Semendyaev AA. **Activity of LPO processes in women with polycystic ovarian syndrome and infertility.** Bull Exp Biol Med. 2017; 162(3):320-2. Available from: doi: 10.1007/s10517-017-3605-5.
2. Arain F, Arif N, Halepota H. **Frequency and outcome of treatment in polycystic ovaries related infertility.** Pak J Med Sci. 2015; 31(3):694. Available from: doi: 10.12669/pjms.313.8003.
3. Shaheen R, Subhan F, Sultan S, Subhan K, Tahir F. **Prevalence of infertility in a cross section of Pakistani population.** Pakistan Journal of Zoology. 2010;42(4).
4. De Leo V, Musacchio MC, Cappelli V, Massaro MG, Morgante G, Petraglia FJ. **Genetic, hormonal and metabolic aspects of PCOS: An update.** Reprod Biol Endocrinol. 2016; 14(1):1-7. Available from: doi: 10.1186/s12958-016-0173-x.
5. Mohammad MB, Seghinsara AM. **Polycystic ovary syndrome (PCOS), diagnostic criteria, and AMH.** Asian Pac J Cancer Prev. 2017; 18(1):17. Available from: doi: 10.22034/APJCP.2017.18.1.17.
6. Escobar-Morreale HF. **Polycystic ovary syndrome: Definition, aetiology, diagnosis and treatment.** Nat Rev Endocrinol. 2018; 14(5):270-84. Available from: doi: 10.1038/nrendo.2018.24.
7. Pasquali R, Diamanti-Kandarakis E, Gambineri A. **Management of endocrine disease: Secondary polycystic ovary syndrome: Theoretical and practical aspects.** Eur J Endocrinol. 2016;175(4):157-69. Available from: doi: 10.1530/EJE-16-0374.
8. Patel S. **Polycystic ovary syndrome (PCOS), an inflammatory, systemic, lifestyle endocrinopathy.** J Steroid Biochem Mol Biol. 2018; 182:27-36. Available from: doi: 10.1016/j.jsbmb.2018.04.008.
9. Rodriguez Paris V, Bertoldo MJ. **The mechanism of androgen actions in PCOS etiology.** Med Sci. 2019; 7(9):89. Available from: doi: 10.3390/medsci7090089.
10. Shi B, Feng D, Sagnelli M, Jiao J, Sun X, Wang X, Li D. **Fructose levels are elevated in women with polycystic ovary syndrome with obesity and hyperinsulinemia.** Hum Reprod. 2020;35(1):187-94. Available from: doi: 10.1210/clinem/dgaa605.
11. Andrae F, Abbott D, Stridsklev S, Schmedes AV, Odsæter IH, Vanky E, Salvesen Ø. **Sustained maternal hyperandrogenism during PCOS pregnancy reduced by metformin in non-obese women carrying a male fetus.** J Clin Endocrinol Metab. 2020;105(12):3762-70. Available from: doi: 10.1210/clinem/dgaa605.
12. Ellakwa HE, Sanad ZF, Hamza HA, Emara MA, Elsayed MA. **Predictors of patient responses to ovulation induction with clomiphene citrate in patients with polycystic ovary syndrome experiencing infertility.** Int J Gynaecol Obstet. 2016; 133(1):59-63. Available from: doi: 10.1016/j.ijgo.2015.09.008. Epub 2015 Dec 17.

13. Iftikhar N, Batool T. **Comparison of the effects of clomiphene citrate alone versus combined metformin and clomiphene citrate in increasing ovulation and fertility in patients with polycystic ovarian syndrome with anovulatory infertility.** J. 2014; 6(1):15-8.
14. Saravelos SH, Regan L. **Unexplained recurrent pregnancy loss.** ObstetGynecolClin. 2014;41(1):157-66. Available from: <https://doi.org/10.1093/humrep/des102>
15. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. **Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: A prospective study.** J Clinical EndocrinolMetabol. 1998;83(9):3078-82. Available from: doi: 10.1210/jcem.83.9.5090.
16. Palomba S, Orio F, Russo T, Falbo A, Cascella T, Colao A, Lombardi G, Zullo F. **Is ovulation induction still a therapeutic problem in patients with polycystic ovary syndrome?.** J. Endocrinol. Invest. 2004;27(8):796-805. Available from: <https://doi.org/10.1007/BF03347527>
17. Hughes E, Brown J, Collins JJ, Vanderkerchove P. **Clomiphene citrate for unexplained subfertility in women. Cochrane database of systematic reviews.** 2010(1). Available from: doi: 10.1002/14651858.CD000057.pub2.
18. Morin-Papunen L, Rantala AS, Unkila-Kallio L, Tiitinen A, Hippeläinen M, Perheentupa A, Tinkanen H, Bloigu R, Puukka K, Ruokonen A, Tapanainen JS. **Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): A multicenter, double-blind, placebocontrolled randomized trial.** J Clin Endocrinol 2012;97(5):1492-500. Available from: doi: 10.1210/jc.2011-3061.
19. Vandermolen DT, Ratts VS, Evans WS, Stovall DW, Kauma SW, Nestler JE. **Metformin increases the ovulatory rate and pregnancy rate from clomiphene citrate in patients with polycystic ovary syndrome who are resistant to clomiphene citrate alone.** Fertility and sterility. 2001; 75(2):310-5. Available from: doi: 10.1016/s0015-0282(00)01675-7.
20. Wang R, Kim BV, Van Wely M, Johnson NP, Costello MF, Zhang H, Ng EH, Legro RS, Bhattacharya S, Norman RJ, Mol BW. **Treatment strategies for women with WHO group II anovulation: Systematic review and network meta-analysis.** bmj. 2017;356. Available from: doi: <https://doi.org/10.1136/bmj.j138>
21. Fatima A, Khan SA, Saifuddin Z, Aslam R. **Comparison of efficacy of clomiphene citrate alone and with metformin for treatment of infertility in polycystic ovarian syndrome.** Rawal Med J. 2018 Apr 1;43(2):285-8.
22. Oriji VK, Nyengidiki K. **Ovulation induction in women with polycystic ovary syndrome: What is the optimal option?.** Debatable Topics in PCOS Patients. 2017.
23. Airao BB, Savalia PJ, Chaudhary RV. **Clomiphene citrate alone versus combined metformin and clomiphene citrate versus combined metformin and clomiphene citrate and drilling versus metformin alone in infertile Indian women with PCOS: A prospective cross-sectional study.** Int Journal ReproductionContraceptObstet Gynecol. 2018; 7(4):1527-32.

AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Syeda Uzma	Data collection, write up, ethical committee presentation, references.	
2	Adiba Akhtar Khalil	Data collection, write up and statistics.	
3	Rabiya Akbar	Data collection, write up, statistics and references.	
4	Tallat Shaheen	Data collection, synopsis and proof reading and references .	