

Efficacy of clomiphene citrate & metformin versus clomiphene alone in the treatment of primary infertility in obese women with polycystic ovarian syndrome

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Abstract

Objective: To compare the efficacy of clomiphene citrate & metformin versus clomiphene alone in the treatment of primary infertility in obese women with polycystic ovarian syndrome.

Study design: Randomized controlled trial

Settings: This study was performed at department of Obstetrics and Gynaecology, Mardan Medical Complex and Teaching Hospital, Mardan from 9th September, 2018 to 9th March, 2019.

Material and Methods: After approval from the ethical committee, a total of 760-females, suffering from PCOS with infertility, were included in the study. All the included women were randomly allocated in two groups by lottery method. Women in group-A were subjected to metformin plus clomiphene citrate. Women in the group-B were only subjected to clomiphene citrate. All the women in both groups were followed up regularly till next 3-months and unprotected intercourse two to three times per week was advised to all women in either groups. Women in both the groups were screened by urinary pregnancy test until 3-months from start of therapy if a woman presents with clinical suspicion of pregnancy.

Results: Average age of the patients was 24.77 ± 8.12 years. Fertility was achieved in 98 (25.8%) cases in group-A while in 68 (17.9%) cases in group-B, which was significantly high in group-A with p -value=0.008.

Conclusion: Metformin plus clomiphene is more effective than clomiphene alone in the treatment of primary infertility due to polycystic ovarian syndrome in obese women.

Keywords: Efficacy, metformin, clomiphene, polycystic ovarian syndrome, primary infertility

Introduction:

Infertility is inability to conceive an offspring when it is wanted. It is best defined as the inability to conceive after one year of unprotected regular intercourse. Based on this, 60–80 million couple all over the world can be labeled as suffering from Infertility.¹ It is of two types: primary infertility and secondary infertility.² Primary infertility: when there is an absence of a preceding pregnancy, and secondary infertility: failure to conceive following a previous pregnancy, irrespective of the outcome.³ Infertility is a major problem affecting women's health and quality of life.⁴ In Pakistan the prevalence of in-

fertility is reported as 21.9%.⁵ The female factors contribute most (40-55%) in the etiologies of infertility followed by male factors (25%), both partners (10%), and unexplained (10%). Major causes of infertility include ovarian dysfunction (32%), tubal disease (20%), endometriosis (22%), uterine or cervical factors (18%).² Untreated pelvic inflammatory disease (16.7%), post-abortal, post-partum infection and tuberculosis are common factors of infertility in developing countries.⁵

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies affecting

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Table 1: Hormonal profile of the study population

Hormone	Group A	Group B
LH	10.36±3.61	13.57±2.19
FSH	9.73±4.58	10.33±4.18
LH/FSH	1.34±0.23	2.11±0.34
Prolactin	20.51±12.14	22.47±7.13
Androgens	20.33±4.16	19.68±9.17

5%–10% of reproductive age women. It was originally described as a triad consisting of obesity, hirsutism, and oligomenorrhea/infertility.⁶ The prevalence of obesity has strongly increased during the last decades⁷ with an estimate of 5% in developing countries and more than 30% in developed countries.⁸ Its consequences on health are numerous, particularly concerning fertility. Overweight and obese women often face with infertility, Polycystic Ovarian Syndrome (PCOS), high miscarriage rate and obstetrical complications during pregnancy, leading to lower live birth rate.⁷

Polycystic ovarian syndrome (PCOS) is the usual etiology of anovulatory infertility and treatment with the insulin sensitizing agent metformin has been proposed as an alternative to clomiphene citrate.^{9,10} Metformin in combination with clomiphene citrate may increase the rate of ovulation and pregnancy, but does not significantly improve the rate of live births over that of the clomiphene citrate alone.

In a study by Zain MM et al, the ovulation rate was 23.7% in the metformin group, 59% in the clomiphene citrate group, and 68.4% in the combination treatment group.⁶ In another study by Johnson NP et al, no evident difference was observed between clomiphene citrate alone or in combination with metformin in women with BMI > 30 kg/m² in terms of clinical pregnancy (15% vs 22%).¹⁰

The aim of this study is to compare the efficacy of clomiphene citrate alone and in combination with metformin in the treatment of primary infertility due to PCOS in obese women. This study will be first of its kind in our local population and the results of this study will generate lo-

cal data in terms of efficacy for both these drugs.

Materials and Methods:

Our study was performed from from 9th September 2018 to 9th March, 2019 in the department of Obstetrics and Gynaecology at Mardan Medical Complex & Teaching Hospital, Mardan. After approval from the ethical committee, all women who fail to achieve conception meeting the inclusion criteria were enrolled in the study through out patient department. A written informed consent was obtained from all patients. All women were subjected to complete history and detailed physical and gynaecological examination to detect and exclude confounders to exclude bias from the study results. Patients were examined by the same radiologist for diagnosis of PCOS. The Rotterdam diagnostic criteria for PCOS include oligo/anovulation, hyper-androgenism (clinical or biochemical) and polycystic ovaries (12 or more follicles of >2-9 mm in diameter and ovarian volume >10ml) on ultrasound. Two of the above three criteria are required. A detailed hormonal profile was done including LH, FSH, Prolactin and androgens. All the included women were randomly allocated in two groups by lottery method. Women in group-A were subjected to metformin plus clomiphene citrate (metformin 850 mg twice daily and clomiphene citrate were given in a dose of 50 mg on days 2–6 and were increased stepwise to a maximum of 100 mg). Women in the group-B were only subjected to Clomiphene citrate as per above mentioned dosage schedule. All the women in both groups were followed up regularly till next three months and unprotected intercourse two to three times per week was advised to all women in either groups. Women in both the groups were screened for urinary pregnancy test until 3-months from start of therapy if a woman presents with clinical suspicion of pregnancy. The efficacy was labeled if positive urinary pregnancy test after 3-months of regular drug intake and unprotected intercourse was achieved. All data were stored and analyzed in SPSS version 21. Chi square test was used to compare the efficacy in both groups while keeping p value of < 0.05 as significant.

Table 2: Comparison of both groups for efficacy

		Group-A	Group-B	Total	p-value
Efficacy	Yes	98 (25.8%)	68 (17.9%)	166 (21.8%)	0.008
	No	282 (74.2%)	312 (82.1%)	594 (78.2%)	
Total		380	380	760	

Chi square test was used to compare the efficacy in both groups and p value was 0.008.

Results:

The mean age of patients was 23.56 ± 9.11 years in group-A while 25.98 ± 7.13 in group-B. The mean duration of PCOS or infertility was 2.36 ± 1.74 years in group-A and 2.21 ± 4.68 years in group-B. The mean BMI of females was $32.33 \pm 4.16 \text{ kg/m}^2$ in group-A and $33.58 \pm 9.63 \text{ kg/m}^2$ in group-B. The hormonal profile of the patients is projected in table 1.

In group-A, efficacy was achieved in 98 (25.8%) cases while in 68 (17.9%) cases in group-B. Fertility improvement was significantly high in group-A with p-value=0.008 (table 2).

Discussion:

Infertility is defined as the failure to conceive after one year of regular intercourse in women < 35 years not using contraception and after 6-months in women > 35 years.¹¹ Epidemiological data suggest that about 10% to 15% of all couples will experience difficulties to conceive (primary infertility). The most common identifiable factors that accounted for female infertility, were ovulatory disorders (25%).

PCOS is associated with approximately 75% of women who suffer from infertility caused by anovulation.¹² It is generally accepted that the first line of treatment to induce ovulation in PCOS women is clomiphene citrate administration. Despite treatment with clomiphene citrate, a variable percentage of PCOS women remains anovulatory or does not achieve a pregnancy. In fact, the ovulation rate after clomiphene citrate treatment is approximately 70–80% with a pregnancy rate of approximately 40%.^{13,14}

Data about the impact of metformin plus clomiphene on pregnancy and delivery rates in women with PCOS are limited. In a study, 33.1% of

obese women in combination group and 30.6% in the clomiphene citrate monotherapy group with primary infertility became pregnant.¹⁵ In another study, investigators reported that the pregnancy rate was 55% in women treated with metformin plus clomiphene compared with 7% in women treated with placebo plus clomiphene.¹⁶ The combination of clomiphene and metformin was superior to clomiphene alone in inducing ovulation in women with PCOS, in 3-randomized clinical trials.¹⁶ In our study, combination therapy was more effective (25.8%) as compared to clomiphene alone (17.9%), further supporting the results of the above mentioned studies.

In a study by Wang R. et al,¹⁷ compared with clomiphene alone, the combination of clomiphene and metformin led to significantly higher pregnancy rates (odds ratio 1.58, 95% confidence interval 1.25 to 2.00; 1.81, 1.35 to 2.42; respectively) similar to the results of our study as well. In terms of live birth, letrozole had the highest efficacy (81%), followed by follicle stimulating hormone (74%), clomiphene and metformin combined (71%), tamoxifen (48%), clomiphene (36%), and metformin (30%), while placebo or no treatment (10%) had the lowest efficacy.¹⁷

In a local study by Ambreen Fatima,¹⁸ 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. This difference may be due to the reduced sample size of 128-patients, 64 in each group in the mentioned study.

Clomiphene citrate in combination with metformin showed a higher pregnancy rate than clomiphene citrate alone or metformin alone. The odds ratio for pregnancy when clomiphene citrate in combination with metformin is compared to clomiphene citrate alone is 1.8 (1.35–2.42) indicating that clomiphene citrate in combination with metformin is a better treatment and offers 1.8 times the chance of pregnancy

compared to the clomiphene citrate alone,¹⁹ further strengthening our results.

In another study by Airao BB et al,²⁰ The ovulatory rate with the metformin and clomiphene citrate combination was found to be significantly higher when compared with clomiphene citrate given alone ($P = 0.0016$) in infertile PCOS subjects. The ovulatory rate was found to be increasing when clomiphene citrate of 150 mg was given in combination with metformin for three cycles. The pregnancy rate was high with the clomiphene citrate and metformin combination when compared with clomiphene citrate alone and even in clomiphene citrate-resistance PCOS. Hence, this combination should be initiated early during treatment.

Our study had average BMI of 32.33 in group-A while 33.58 in group-B which shows the prevalence of obesity in our population & that weight reduction in itself could be of benefit in achieving pregnancy. It is logical to use monotherapy as first line treatment with either metformin alone or clomiphene alone. In an English study by Morley et al,²¹ Metformin appears to have a limited role in improving reproductive outcomes in women with PCOS, although there may be a benefit to using metformin in specific patient groups, for example in obese women when combined with clomiphene citrate, those with clomiphene citrate resistance, and those who have been found to have either IGT or type-II diabetes. This also support our results that the combination of metformin and clomiphene citrate is more effective in achieving pregnancy than clomiphene citrate alone.

Conclusion:

There was significant difference between the metformin plus clomiphene and clomiphene alone in the treatment of primary infertility due to polycystic ovarian syndrome in obese women. Combination therapy is better than when using clomiphene alone. Thus combination therapy is recommended for primary infertility due to polycystic ovarian syndrome in obese women.

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Role and contribution of authors:

Dr. Fatima, collected the data, references and did the initial writeup.

Dr. Noorul Amina, collected the data and helped in introduction writing.

Dr. Nabila Khan, collected the data and helped in methodology writing

Dr. Hemasa Gul, collected the references and helped in tabulation of data and result writing.

Dr. Shah Muhammad Khan, collected the references and helped in discussion writing.

Dr. Anila Hayat, critically review the article and made final changes.

References:

1. Khan SJ, Gulab N, Khan PJ. Frequency of pelvic inflammatory diseases among women presenting with infertility. *KJMS* 2014;7(1):0346-9033380.
2. Boricha Y, Sharma R. Laparoscopy in 50 infertile couples: prospective study. 2011.
3. Ghazi A, Saddique M, Siddiq N, Jabbar S, Ali T, Jaipal S. Subfertility: experience in a tertiary care hospital. *Pak J Surg* 2007;23(4):283-6.
4. Naz T, Hassan L, Gulmeen NF, Sultan S. Laparoscopic evaluation in infertility. *J Coll Physicians Surg Pak* 2009;19(11):704-7.
5. Aziz N. Laparoscopic evaluation of female factors in infertility. *J Coll Physicians Surg Pak* 2010;20(10):649-52.
6. 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. *Fertility and sterility* 2009;91(2):514-21.
7. Leperlier F, Lammers J, Dessolle L, Lattes S, Barrière P, Fréour T. No evidence of early embryo development modification in obese women compared with non obese women as reflected by time lapse analysis: P-298. *Human Reproduction* 2012;27.
8. Maheshwari A, Scotland G, Bell J, McTavish A, Hamilton M, Bhattacharya S. The direct health services costs of providing assisted reproduction services in overweight or obese women: a retrospective cross-sectional analysis. *Human reproduction* 2008;24(3):633-9.
9. Richards G, Levy H, Laterre P-F, Feldman C, Woodward B, Bates BM, et al. CURB-65, PSI, and APACHE II to assess mortality risk in patients with severe sepsis and community acquired pneumonia in PROWESS. *Journal of intensive care medicine* 2011;26(1):34-40.
10. Johnson N, Stewart A, Falkiner J, Farquhar C, Milsom S, Singh V-P, et al. PCOSMIC: a multi-centre randomized trial in women with PolyCystic Ovary Syndrome evaluating Metformin for Infertility with Clomiphene. *Human reproduction* 2010;25(7):1675-83.
11. Sarvelos SH, Regan L. Unexplained recurrent pregnancy loss.

- Obstetrics and Gynecology Clinics 2014;41(1):157-66.
12. Knochenhauer E, Key T, Kahsar-Miller M, Waggoner W, Boots L, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *The Journal of Clinical Endocrinology & Metabolism* 1998;83(9):3078-82.
 13. Palomba S, Orio F, Russo T, Falbo A, Cascella T, Colao A, et al. Is ovulation induction still a therapeutic problem in patients with polycystic ovary syndrome? *Journal of endocrinological investigation* 2004;27(8):796-805.
 14. Hughes E, Brown J, Collins JJ, Vanderkerchove P. Clomiphene citrate for unexplained subfertility in women. *Cochrane database of systematic reviews* 2010(1).
 15. Morin-Papunen L, Rantala AS, Unkila-Kallio L, Tiitinen A, Hippeläinen M, Perheentupa A, et al. Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial. *The Journal of Clinical Endocrinology* 2012;97(5):1492-500.
 16. 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.
 17. Fux Otta C, Wior M, Iraci GS, Kaplan R, Torres D, Gaido MI, et al. Clinical, metabolic, and endocrine parameters in response to metformin and lifestyle intervention in women with polycystic ovary syndrome: a randomized, double-blind, and placebo control trial. *Gynecological Endocrinology* 2010;26(3):173-8.
 18. Karimzadeh MA, Javedani M. An assessment of lifestyle modification versus medical treatment with clomiphene citrate, metformin, and clomiphene citrate–metformin in patients with polycystic ovary syndrome. *Fertility and sterility* 2010;94(1):216-20.
 19. Al-Inany H, Johnson N. Drugs for anovulatory infertility in polycystic ovary syndrome. *British Medical Journal Publishing Group*; 2006.
 20. Tang T, Glanville J, Hayden CJ, White D, Barth JH, Balen AH. Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo-controlled, double-blind multicentre study. *Human reproduction* 2005;21(1):80-9.
 21. Kashyap S, Wells GA, Rosenwaks Z. Insulin-sensitizing agents as primary therapy for patients with polycystic ovarian syndrome. *Human Reproduction* 2004;19(11):2474-83.
 22. Wang R, Kim BV, Wely MV, Johnson NP, Costello ME, Zhang H, Yu 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. *British medical journal* 2017;356:j138.
 23. 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 Medical Journal* 2018; 43(2): 287.
 24. Orijji VK & Nyengidiki K. Ovulation Induction in Women with Polycystic Ovary Syndrome: What is the Optimal Option? *Debatable topics in PCOS Patients* 2017; Neeraj Kumar Agrawal & Kiran Singh, IntechOpen, DOI: 10.5772/intechopen.70812.
 25. 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 J Reprod Contracept Obstet Gynecol* 2018;7:1527-31.
 26. Morley LC, Tang TMH & Balen AH. Metformin Therapy for the Management of Infertility in Women with Polycystic Ovary Syndrome. *The British Journal of Obstetrics and Gynaecology* 2017 ; 124 (12) : e306-e313.