

# Comparision Between the Efficacy of Metformin Plus Clomiphene and Clomiphene Alone in the Treatment of Primary Infertility Due to Polycystic Ovarian Syndrome in Obese Women

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## ABSTRACT

**Background:** Infertility is defined as the inability to conceive after one to two years of unprotected intercourse. It is of two types primary infertility and secondary infertility Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies affecting 5%–10% of reproductive age women. To compare the efficacy of metformin plus clomiphene and clomiphene alone in the treatment of primary infertility due to polycystic ovary syndrome in obese women

**Materials And Methods:** It was Randomized Controlled Trial, which was conducted in the department of Obstetrics and Gynaecology, Hospital, Peshawar, between 30<sup>th</sup> May 2019 to 8<sup>th</sup> January 2022) Sample size will be 380 in each group using P 1 = 15%, P 2 = 22% and power of 80% and 95% confidence interval under WHO Software for sample size determination.

**Results:** A total of 380 patients in each group were observed. Average age of the patients was 26.60 years+ 3.99SD with range of 19-35 years. Group A showed 88(23.2%) efficacies. Similarly Group B showed 68 (17.9%) efficacies. Efficacy was significant in both the groups with p-value=0.044.

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

**Keywords:** Efficacy, metformin, clomiphene, polycystic ovary 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.<sup>1</sup> Infertility is of two types i.e. primary- when there is an absence of a preceding pregnancy, and secondary- failure to conceive following a previous pregnancy, irrespective of the outcome.<sup>2</sup> Infertility is a major problem affecting women's health and quality of life.<sup>3</sup> In Pakistan the prevalence of infertility is reported as 21.9%.<sup>4</sup> 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%).<sup>5</sup> Untreated pelvic inflammatory disease (16.7%), post-abort, postpartum infection and tuberculosis are common factors of infertility in developing countries.<sup>4</sup> As most of our patients are illiterate and from low socio-economic class,<sup>6</sup> most of the patients usually go to quacks for treatment of infertility which lead to further worsening and delay in proper management.<sup>7</sup> Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies affecting 5%–10% of reproductive age women. It was originally described as a triad consisting of obesity, hirsutism, and oligoamenorrhea/infertility<sup>8</sup>. The prevalence of obesity has strongly increased during the last decades<sup>9</sup> with an estimate of 5% in developing countries and >30% in developed countries<sup>10</sup>. 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<sup>9</sup>. Polycystic ovary 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 (CC)<sup>11</sup>. Metformin in combination with CC may increase the rate of ovulation and pregnancy, but does not significantly improve the rate of live births over that of the CC alone. Metformin can be also added to CC in women who show resistance to clomiphene, who are older and/or have visceral obesity<sup>12</sup>. However, the role of metformin in the treatment of infertility in women with polycystic ovary syndrome (PCOS) is still controversial<sup>13</sup>. Early systematic reviews of randomized controlled trials (RCTs) showed that metformin was more effective than

placebo for inducing ovulation, however, these trials and systematic reviews were vastly underpowered to detect differences in clinically relevant outcomes such as pregnancy and live birth<sup>14</sup>. The addition of metformin to CC in combination therapy was proven to be more effective than CC alone only among women with known CC resistance<sup>11</sup>.

In one study by Johnson NP et al, no evident difference was observed between CC alone or in combination with metformin in women with BMI > 30 kg/m<sup>2</sup> in terms of clinical pregnancy (15% vs 22%)<sup>11</sup>. In another study, no difference was observed in fertility improvement between the combination treatment and CC monotherapy (P = 0.982) and they concluded that no guideline can be given regarding use of any kind of combination or monotherapy with metformin or CC<sup>15</sup>. In another study, 33.1% of obese women in combination group and 30.6% in the CC monotherapy group with primary infertility became pregnant<sup>13</sup>. In another study, the ovulation rate was 23.7% in the metformin group, 59% in the CC group, and 68.4% in the combination treatment group<sup>8</sup>. The aim of this study is to compare the efficacy of CC alone and in combination with metformin 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 local data in terms of efficacy for both these two drugs.

## MATERIALS AND METHODS

It was Randomized Controlled Trial, which was conducted in the department of Obstetrics and Gynecology, Hospital, Peshawar, between 30<sup>th</sup> May 2020 to 8<sup>th</sup> January 2021) Sample size will be 380 in each group using P 1 = 15%, P 2 = 22%<sup>11</sup> and power of 80% and 95% confidence interval under WHO Software for sample size determination. Data was collected through non probability (consecutive) sampling technique. All women presenting with primary infertility with clinical and ultrasonographic diagnosis of PCOS and BMI of more than 30kg/m<sup>2</sup>.and reproductive age group (15-35 years) were included in the study. All the patients with history of use of intrauterine contraceptive devices. And Women with history of hormonal disturbances, i.e. thyroid, adrenal and other causes of hyperandrogenism were excluded from the study.

The study was conducted after approval form hospitals research and ethical board. All women who fail to achieve conception (as per operational definitions above) meeting the inclusion criteria were enrolled in the study through OPD. The purpose and benefits of the study were explained to the patients

and they were assured that the study is done purely for data publication and research purpose and their confidentiality were maintained, a written informed consent was obtained from all patients. All women were subjected to complete history taking and detailed physical and gynecological 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, hyperandrogenism (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 850mg 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 group. 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. All data were stored and analyzed in SPSS version 22.0. Mean + SD were calculated for quantitative variables like age. Frequencies and Percentages were calculated for categorical variables like efficacy. Chi square test was used to compare the efficacy in both groups while keeping p value of < 0.05 as significant. Efficacy in both groups was stratified among age to see the effect modification. All results were presented in the form of tables and graphs.

**RESULTS**

A total of 720 patients were observed, which were divided in two equal groups A & B. Patients in Group A were managed with metformin plus clomiphene citrate (metformin 850mg 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 alone. BMI wise distribution shows that out of 380 patients 280(73.7%) were having less than or equal to 45 and 100(26.3%) were more than 45 while group B contains 276(72.6%) patients have less than or equal to 45 and 104(34.3%) were more than 45. BMI distribution among the groups was insignificant with p-value=0.403. (Table 1). Average age was 26.60 years+ 3.99SD with range of 19-35 years. Group A contained 24 (6.3%) patients in less than 20 years, 292(76.8%) patients 21-30 years and 64(16.8%) patients between the ages of more than 30 years. While group B contained 27(7.1%) patients in less than or equal to 20 years, 281(73.9%) in 21-30 years and 72(18.9%) patients with age more than 30 years.

The age distribution among the group was also insignificant with p-value 0.651. (Table 2). Efficacy wise distribution shows that Group A showed 88(23.2%) efficacies while non-effective in 292(76.8%) patients. Similarly Group B showed 68(17.9%) efficacies while non effective in 312(82.1%) patients. Efficacy was significant in both the groups with p-value=0.044. (Table 3). Age wise distribution of efficacy in both the groups shows that efficacy was greater in younger age group and decreases with the increase of age. The patients having less than or equal to 20 years of age have shows efficacy in 6(25%) patients in group A while 7(25.9%) patients being effective in group B. Patients with 31-45 years of age have shown efficacy in 66(22.6%) of patients in Group A and 46(16.4%) have shown efficacy in Group B. Similarly, 16(25%) patients have shown efficacy in Group A and 15(20%) patients have efficacy in Group B, with age more than 45 years of age. The age wise efficacy was insignificant with p-value=0.40,0.897 and 0.358 respectively. (Table 4). When efficacy was stratified among the BMI in both the groups it showed in-significance with p-value=0.181,0.172 and 0.188 respectively. There were 60(21.4%)

patients having less than 45 BMI showing efficacy in Group A while effectiveness in 45(16.3%) patients. BMI wise stratification also insignificant in both the group with p-value=0.181 and 0.188 respectively. (Table 5).

Table 1: Bmi Wise Comparison Of Both The Groups

BMI (kg/m2)	Groups		Total	P-value
	A	B		
<= 45.00 46.00+	280	276	556	0.743
	73.7%	72.6%	73.2%	
	100	104	204	
	26.3%	27.4%	26.8%	
Total	190	190	380	
	100.0%	100.0%	100.0%	

Table 2: Age Wise Distribution In Both The Groups

Age (in years)	Group		Total	p-value
	A	B		
<= 20.00 21.00 - 30.00 31.00+	24	27	51	0.651
	6.3%	7.1%	6.7%	
	292	281	573	
	76.8%	73.9%	75.4%	
	64	72	136	
Total	16.8%	18.9%	17.9%	
	380	380	760	
	100.0%	100.0%	100.0%	

Table 3: Efficacy Wise Distribution of Patients In Both The Groups

Efficacy	Groups		Total	P-value
	A	B		
Yes No	88	68	156	0.044
	23.2%	17.9%	20.5%	
	292	312	604	
	76.8%	82.1%	79.5%	
Total	380	380	760	
	100.0%	100.0%	100.0%	

Table 4: Age Wise Distribution Of Efficacy In Both The Groups

Age (in years)	Group				P-value
	A		B		
	Efficacy		Efficacy		
	Yes	No	Yes	No	
<= 20.00	6	18	7	20	0.897
	25.0%	75.0%	25.9%	74.1%	
21.00 - 30.00	66	226	46	235	0.172
	22.6%	77.4%	16.4%	83.6%	
31.00+	16	48	15	57	0.358
	25.0%	75.0%	20.8%	79.2%	

Table 5: BMI Wise Distribution Of Efficacy

BMI (kg/m2)	Group				P-value
	A		B		
	Efficacy		Efficacy		
	Yes	No	Yes	No	
<= 45.00	60	220	45	231	0.181
	21.4%	78.6%	16.3%	83.7%	
46.00+	28	72	23	81	0.188
	28.0%	72.0%	22.1%	77.9%	

## DISCUSSION

Infertility is defined as the failure to conceive after one year of regular intercourse in women < 35 years not using contraception and after six months in women > 35 years<sup>14</sup>. Epidemiological data suggest that about 10% to 15% of all couples will experience difficulties to conceive (primary infertility). Based on a survey performed in developed countries, the World Health Organization (WHO) estimates that female infertility accounts for 37% of causes in infertile couples, male infertility for 8% and both – male and female infertility – for 35%. Five percent of couples have unexplained infertility and 15% became pregnant during the study. The most common identifiable factors that accounted for female infertility, were ovulatory disorders (25%). Other reports describe ovulatory disorders as responsible for more than half of the causes of female infertility<sup>14</sup>. PCOS is associated with approximately 75% of women who suffer from infertility caused by anovulation<sup>14</sup>. It is generally accepted that the first line of treatment to induce ovulation in PCOS women is CC administration. Despite treatment with CC, a variable percentage of PCOS women remains anovulatory or does not achieve a pregnancy. In fact, the ovulation rate after CC treatment is approximately 70–80% with a pregnancy rate of approximately 40 %.<sup>15</sup>

Data about the impact of metformin plus clomiphene on pregnancy and delivery rates in women with PCOS are limited. In 1 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.<sup>15</sup> The combination of clomiphene and metformin was superior to clomiphene alone in inducing ovulation in women with PCOS, in 3 randomized clinical trials.<sup>15</sup> Otta et al., 2010<sup>16</sup> in a randomized, double-blind, and placebo control trial compared lifestyle modification and 1500 mg of metformin or placebo for 4 months in 30 women with insulin resistance PCOS. They reported that metformin has an additive effect to diet and exercise to improve parameters of hyperandrogenism and insulin resistance. However, a small decrease in body weight through lifestyle changes could be enough to improve menstrual cycles in these women. Karimzadeh & Javedani, 2010 (31) in another randomized double-blind study compared lifestyle modification with medical treatment plans such as CC, metformin, and CC with metformin in 343 overweight infertile women with PCOS. They showed that metformin or metformin with CC does not cause a significant weight loss or an improvement in the endocrine status of PCOS women. However, lifestyle modification to reduce waist circumference and body weight could improve their menstrual cycles, hormonal status and was an effective treatment for ovulation induction in those patients with an ovulation and pregnancy rates of 66.6% and 20% respectively.<sup>17</sup>

It is logical to use monotherapy as first line treatment with either metformin alone or clomiphene alone. In spite of many RCTs examining the potential benefit of combined therapy, no clear benefit has been found in RCTs of dual therapy over monotherapy<sup>18</sup>. The live birth rate was not improved amongst 907 women in a meta-analysis who were randomized to clomiphene plus metformin versus clomiphene alone (Peto OR 1.16, 95% CI, 0.85 to 1.56)<sup>19</sup>. Although the clinical pregnancy rate was significantly higher in women receiving dual therapy versus clomiphene alone (Peto OR 1.51, 95% CI, 1.17 to 1.96, from meta-analysis of 1,208 women in RCTs who had this outcome assessed)<sup>19</sup> The most recent research synthesis revealed that metformin was 50% better than placebo for increasing ovulation in infertile women with PCOS and that metformin plus clomiphene citrate may be three to four-fold superior to clomiphene citrate alone for producing ovulation and achievement of pregnancy<sup>16</sup>. The same study, however, showed that metformin alone had no confirmed benefit over placebo for achievement of pregnancy. Also support our results that the combination of metformin and

clomiphene citrate is more effective in achieving pregnancy than clomiphene citrate (CC) alone.<sup>20</sup>

## CONCLUSION

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

## REFERENCES

- Haider G, Rani S, Talpur S, Zehra N, Munir A. Laparoscopic evaluation of female infertility. *J Ayub Med Coll Abbottabad*. 2022;22(1):136-8.
- Ghazi A, Saddique M, Siddiq N, Jabbar S, Ali T, Jaipal S. Subfertility: Experience in a tertiary care hospital. *Pak J Surg*. 2017;23(4):283-6.
- Naz T, Hassan L, Gulmeen, Nighat F, Sultan S. Laparoscopic evaluation in infertility. *J Coll Physicians Surg Pak*. 2019;19(11):704-7.
- Aziz N. Laparoscopic evaluation of female factors in infertility. *J Coll Physicians Surg Pak*. 2018;20(10):649-52.
- Boricha YG, Sharma RK, Boricha BG, Mhapankar S, Chaterjee A, Narshetty J. Laparoscopy in 50 infertile couples: prospective study. *IJMCR*. 2017;2(2):63-6.
- Talib W, Ikram M, Hafeez M, Saeed M. Infertile female; laparoscopic evaluation. *Professional Med J*. 2017;14(4):562-6.
- Parveen S, Khanam M. Role of combined diagnostic laparoscopy and simultaneous diagnostic hysteroscopy for evaluation of female subfertility factors. *J Surg Pak*. 2018;15(1):44-7.
- 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* 2019;91(2):514-22.
- Leperlier F, Lammers J, Dessolle L, Lattes S, Barrière P, Fréour P. P-298 No evidence of early embryo development modification in obese women compared with non obese women as reflected by time lapse analysis. *Hum Reprod*. 2019;27(2):226-47.
- Maheshwari A, Scotland G, Bell J, McTavish A, Hamilton M, Bhattacharya S. The direct health services costs of providing assisted reproductive services in overweight or obese women: a retrospective cross-sectional analysis. *Hum Reprod*. 2019;1:1-8.
- Johnson NP, Stewart AW, Falkiner J, Farquhar CM, Milsom S, Singh VP. PCOSMIC: a multi-centre randomized trial in women with Polycystic Ovary Syndrome evaluating Metformin for Infertility with Clomiphene. *Hum Reprod*. 2019;25(7):1675-83.
- Tomic V, Tomic J. Infertility Treatment in Patients with Polycystic Ovary Syndrome (PCOS). *J Fertiliz In Vitro*. 2022;2:2
- Morin-Papunen L, Rantala AS, Unkila-Kallio L, Tiitinen A, Hippela 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. *J Clin Endocrinol Metab*. 2019;97(5):1492–500.
- Creanga AA, Bradley HM, McCormick C, Witkop CT. Use of metformin in polycystic ovary syndrome—a meta-analysis. *Obstet Gynecol*. 2008;111:959-68
- Palomba S, Pasquali R, Orio F, Nestler JE. Clomiphene citrate, metformin or both as first-step approach in treating anovulatory infertility in patients with polycystic ovary syndrome (PCOS): a systematic review of head-to-head randomized controlled studies and meta-analysis. *Clin Endocrinol* 2019;70(2):311–21.
- Trussell J, Wilson C. Sterility in a population with natural fertility. *Popul Stud*. 1985;29:269-86.
- Matthiesen SM, Frederiksen Y, Ingerslev HJ, Zachariae R. Stress, distress and outcome of assisted reproductive technology (ART): a meta-analysis. *Hum Reprod*. 2019.
- DeCherney AH, Cholst I, Naftolin F. Structure and function of the fallopian tubes following exposure to diethylstilbestrol (DES) during gestation. *Fertil Steril*. 2011;36(6):741-5.
- Hoover RN, Hyer M, Pfeiffer RM, et al. Adverse health outcomes in women exposed in utero to diethylstilbestrol. *N Engl J Med*. 2011;365(14):1304-14.
- Frisch RE, Revelle R. Height and weight at menarche and a hypothesis of menarche. *Arch Dis Child*. 20120;46(249):695-701.