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Original Research Article

Effect between Clomiphene Citrate plus Metformin and Clomiphene Citrate Alone on Induction of Ovulation in Women with Polycystic Ovarian Syndrome

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Abstract:

Background: PCOS is a common metabolic and reproductive disorder that affects women and causes its symptoms and signs. It is estimated that 4% of women of reproductive age worldwide are affected; however, in populations with a higher risk, some estimates place the percentage closer to 10%. Aim of this study is to determine and compare the rates of ovulation, menstrual cycle regularization, and pregnancy in PCOS patients taking both clomiphene citrate and metformin in combination and clomiphene citrate alone.

Methods: Between March 2023 and February 2024, 220 patients, 110 in each group, with primary subfertility and PCOS diagnoses who were between the ages of 18 and 40 were selected. The primary outcome, or the incidence of ovulation, was determined by folliculometry. Secondary outcomes that were compared between the two groups were the regularization of the menstrual cycle and the frequencies of pregnancy.

Results: Overall ovulation was shown to be at its maximum during the third cycle of ovulation induction, occurring in each group at 48.8% and 41%, respectively. The primary outcome for group A was significantly higher (83.3%) when clomiphene citrate and metformin were administered jointly than when clomiphene citrate was administered alone (65.9%). The secondary results were significantly greater (89.6%) in the group that received metformin with CC. Pregnancy rates were higher in the first group (33.3%) than in the second (20.5%).

Conclusion: Two groups were given varying quantities of clomiphene citrate in this study: one group had it in addition to metformin, while the other group received it just to induce ovulation. It was found that clomiphene citrate plus metformin was a better way to induce ovulation in women with PCOS than clomiphene citrate alone.

Keywords: Metformin, Clomiphene citrate, Ovulation induction, PCOS.

Introduction

Between 4% and 12% of women suffer with polycystic ovarian syndrome (PCOS), the most prevalent endocrinological condition. [1] It has been shown to be the main cause of infertility in women. [2] Clinical characteristics of PCOS are irregular menstruation accompanied by anovulatory infertility and hyperandrogenism. [3] Over time, it became evident that the disease was quite diversified and had a wide range of clinical manifestations. Instead of being considered an illness, it is considered a syndrome. Approximately 69% of affected females had hirsutism, 74% had infertility, 40% were obese, slightly over 50% had amenorrhea, 29% had functional bleeding, and 12% had cyclical menses, according to data gathered from the literature on about 1,080 cases. Insulin and testosterone levels were discovered to be strongly correlated in PCOS. It was evident that IR is only a common feature of the sickness and has nothing to do with obesity. "A tissue, cell, or organism condition where a higher amount of insulin than usual is required to grab quantitatively regular response" and maintain the normal range of glucose levels is the conventional definition of insulin resistance. Between 50 and 70 percent of women with PCOS have IR, which is essential to the pathophysiology of the condition. [4-5] because the ovary's circulating insulin levels rise when the body's insulin levels are above normal, it is thought that this causes redundant anovulation and androgen production. [6] Insulin sensitizing drugs show potential in the treatment of PCOS when administered to insulin-resistant pa-

tients. By improving target tissue response to insulin, these compounds reduce the need for compensatory hyperinsulinemia. [7] Additionally, they promote weight loss, which aids in the resumption of ovulatory cycles in overweight PCOS patients. Biguanides and thiazolidinediones are insulin-sensitive medications that are currently on the market. Among these, women with PCOS who use metformin have higher levels of sponataneous ovulation, menstrual cyclicity, and ovulatory response to CC [8].
As a result, metformin, either alone or in combination with clomiphene citrate, is currently recommended as the initial treatment for infertile women with PCOS [9].

This study intends to elucidate the role that combination therapy comprising metformin and clomiphene citrate plays in promoting ovulation in PCOS patients, as the optimal strategy for doing so is still unclear. The aim of this study is to compare the efficacy of clomiphene citrate alone against clomiphene citrate plus metformin in causing ovulation in PCOS individuals who are infertile or subfertile. The study premise is that, when combined with metformin, clomiphene citrate is more effective than clomiphene citrate alone at inducing ovulation in PCOS patients.

Material and Methods

From March 2023 to February 2024, a randomized double-blind clinical trial was carried out in the obstetrics and gynecology outpatient department at Darbhanga Medical College and Hospital in Laheriasarai, Bihar. Women between the ages of 18 and 40 who had provided their consent and had been diagnosed with PCOS and primary subfertility due to anovulation were included in the study.

PCOS patients not wanting pregnancy, Other detected factors of infertility of women like tubal factors, any known cases of endometriosis, anatomical defect in uterus, any tumour, etc., unexplained vaginal bleeding and AUB, known endocrinopathies like thyroid disorders and hyperprolactinemia, any associated known major medical comorbidities like heart disease and liver disease etc. and male factor of infertility ruled out by husband's semen analysis were excluded from this study.

Consecutive patients were taken as study population following the inclusion and exclusion criteria, and by this way 110 patients were placed in one group, other 110 patients in another group.

Statistical data was expressed as number and percentage. Mean and standard deviation (SD) were calculated where required. Microsoft excel and GraphPad, Quickcals & MedCalc software had been used for statistical calculation. Continuous variables were compared with Student's t-test, categorical variables with Chi-square test; and p value < 0.05 was considered as statistically significant.

Results

Two groups of 220 PCOS patients with primary subfertility were assigned at random. A total of 110 patients from each group 96 from group A and 88 from group B were analyzed for the study.

Table 1: Distribution of cases

Group	No. of cases	Percentage
Clomiphene citrate + metformin	96	52.17%
Clomiphene citrate only	88	47.82%
Total	184	100.00%

Women in Group A were given a single 50 mg tablet of clomiphene citrate and a 500 mg tablet of metformin twice a day to induce ovulation from day three to day seven of the menstrual cycle. Women in Group B were given the identical ovulation-induction protocol as those in Group A, which involved taking a 50 mg pill of clomiphene citrate alone. (Table 1)

Table 2: Association of age of patients in two groups

	Groups		
	Clomiphene citrate + metformin (n=48)	**Clomiphene citrate only (n=44)**	**p-value (t-test)**
Age (in years) [Mean±SD]	25.23±4.01	26.57±4.62	
	No. (%)	**N (%)**	
17-24	30(31.3%)	26(29.5%)	0.16
25-32	54(56.3%)	42(47.7%)	
33-38	12(12.5%)	20(22.7%)	

Analyzing the patients' age distribution revealed that the largest group of patients were between the ages of 25 and 32, followed in decreasing order by those between the ages of 17 and 24 and 33 and 38 (Table 2). There was no statistically significant difference between the two groups.

Table 3: Association of menstrual history in two groups

	Groups		
	Clomiphene citrate + met-formin (n=48)	**Clomiphene citrate only (n=44)**	**p-value (t-test)**
Menstrual history	**No. (%)**	**N (%)**	0.64
Irregular	78(81.3%)	66(75.0%)	
Regular	18(18.8%)	22(25.0%)	

It was found that most of the participants in this study experienced irregular menstrual cycles. There was no statistically significant difference between the two groups' menstrual histories. (Table 3)

Table 4: Association of BMI (normal/overweight/obese) in two groups

	Groups		
	Clomiphene citrate + met-formin (n=48)	**Clomiphene citrate only (n=44)**	**p-value (t-test)**
BMI (Normal/ over-weight/obese) [Mean±SD]	28.66±3.89	28.0±4.18	
	No. (%)	**N (%)**	0.43
Normal (18.5-24.9)	12(12.5%)	20(22.7%)	
Overweight (25-29.9)	40(41.7%)	36(40.9%)	
Obese (>30)	44(45.8%)	32(36.4%)	

Prior to having a normal BMI (12.5% in the first group, 22.7% in the second), the majority of patients were obviously obese (45.8% in the first group, 36.4% in the second), followed by overweight (41.7% in the first group, 40.9% in the second group). There was no statistically significant difference between the two groups. (Table 4)

Table 5: Fasting sugar and OGTT in two groups

	Groups		
	Clomiphene citrate + metformin (n=48)	**Clomiphene citrate only (n=44)**	**p-value (t-test)**
FBS and OGTT	**No. (%)**	**N (%)**	0.02
Deranged	34(35.4%)	54(61.4%)	
Normal	62(64.6%)	34(38.6%)	

Patients in both groups were given an oral glucose tolerance test using 75 grams of glucose. The second group (CC alone) had a substantially higher incidence of abnormal OGTT (61.4%) than the first group (35.4%). In Table 5, the P-value is less than 0.05. The first group's mean LH:FSH ratio was 2.79±0.65, whereas the second group was 2.81±0.62.

Regarding the LH: FSH ratio, there is no discernible statistically significant difference between the two groups. On Day 21 of the menstrual cycle, two groups underwent serum progesterone induction on the first cycle of ovulation. The first group's mean progesterone value was 4.22±4.99, while the second group's mean was 4.05±3.84.

Regarding the assessment of serum progesterone in the two groups, there was no statistically significant difference. The mean progesterone values in the first and second groups during the third cycle of ovulation induction were 5.98±4.48 and 6.17±4.38, respectively. Regarding the assessment of serum progesterone in the two groups, there was no statistically significant difference. In the sixth cycle of ovulation induction, the mean progesterone values in the first group were 8.73±6.47, while in the second group they were 5.9±5.28. Between the two groups, there was no statistically significant difference in the assessment of serum progesterone.

First group of patients received a combination of clomiphene citrate and metformin for ovulation induction, whereas second group received clomiphene citrate alone. During the first cycle of therapy, follicular monitoring was performed on both patient groups, and ovulation evidence was observed. Folliculometry showed that the first group of patients had more ovulation evidence (18.8%) than the second group (11.4%). In the first cycle of folliculometry, there is no statistically significant difference observed between the two groups regarding ovulation evidence.

Folliculometry performed during the third cycle of ovulation induction revealed more ovulation evidence in the first group (48.8%) than in the second group (41%). Between the two groups, there was no statistically significant difference. In

the sixth cycle of ovulation induction, the first group of patients showed more evidence of ovulation by folliculometry (50%) than the second group (34.8%). Between the two groups, there is no statistically significant difference.

After the recommended treatment was finished in both groups, an overall analysis was conducted to determine the frequency of ovulation. The results showed that the first group had a greater ovulation rate (83.3%) than the second group (65.9%). The first group ovulation induction was noticeably higher than the second group's. P-value is equal to 0.0001.

Menstrual cycle was regularized in patients treated with CC plus Metformin (89.6%), compared to patients treated with CC alone (38.6%). Menstrual cycle regularization was substantially higher in the first group. (P-value less than 0.05).

Compared to the second group (20.5%), the first group pregnancy rate was slightly greater (33.3%). The pregnancy rates in the two groups did not differ statistically significantly.

After the third treatment cycle, the majority of patients ovulated, and the first group overall ovulation rate was higher than the second group. The difference in ovulation rates between the two groups' treatment cycles did not reach statistical significance.

Discussion

The majority of the patients in this study were in the 25–32 age range. Of these, 47.7% were in group B and 56.3% were in group A. The relative means for each group were 26.57±4.62 and 25.23±4.01. There was no statistically significant difference in the patients' ages between the two groups (P-value = 0.16). The Hardik Patel et al., [10] study's mean age distribution was 26.04±7.78, which was similar to what we found. The proportion of those over 31 was only 8.33%. Similar results were obtained by Legro et al. study [11], which showed a mean age distribution of 27.9±4.

Rural areas accounted for 64.6% and 65.9% of the patients in the first and second groups of this study, respectively. While comparable between the two groups, other characteristics such as menstruation history and socioeconomic level were not statistically significant.

With mean values of 28.66±3.89 and 28±4.18, respectively, the majority of patients in our study had an obesity BMI of 48.5% in the first group and 36.4% in the second. 12.5% and 22.7% of the previously indicated groups, respectively, had a BMI of less than 25 kg/m^2. The study conducted by Hardik Patel et al. found that twenty patients (41.67%) had a body mass index (BMI) of less than 25 kg/m^2, whereas twenty-eight patients (58.33%) had a BMI of more than 25 kg/m2. [10] A study by Papa Dasari et al. [12] found that 37.5% of the patients had obesity, which is very similar to what we found. Moll et al. carried out some comparable research, but the Dunaif et al. [13] study found a higher incidence of obesity (55.87%) and (65%) in the relevant order of medication when compared to our study.

Acne-like symptoms were seen in 18.8% of patients in Group A and 18.2% of patients in Group B in the current investigation. On average, 38.3% of patients in both groups had hirsutism, according to the Ferriman Gallway Scale [14]; however, the differences were not statistically significant.

According to a study by Hardik Patel et al., 45.83% of patients had acne and 56.25% of patients had hirsutism. [10]. A research by Papa Dasari et al. [12] reported that 85% of subjects had hirsutism. These studies revealed a greater prevalence of hirsutism in PCOS patients than ours did.

Although our study included a liver function test, lipid profile, and USG of the entire abdomen, there were no statistically significant changes between the two groups.

We conducted an oral glucose tolerance test and assessed fasting blood sugar (mg/ml) as part of our investigation. On average, 48.4% of patients in both groups were found to be disturbed. Differences between the two groups were statistically significant in both OGTT and FBS (p-value=0.02).

The 21st day of the menstrual cycle, or the premenstrual period, is when serum progesterone was measured. >3ng/ml values signify ovulation. At the conclusion of the sixth cycle of ovulation induction, the mean serum progesterone in the first group (8.73 ± 6.47ng/mL) was found to be the highest in this study. The mean progesterone in the second group peaked at the conclusion of the third cycle of ovulation induction, at 6.17±4.38 ng/mL. Between the two groups, there was no discernible difference. Israel et al. [15] discovered that in patients exhibiting signs of ovulation, blood progesterone was (>=3ng/ml) during the premenstrual period. Similarly, Nadji et al. [16] found that secretory endometrium, which in turn signified ovulation, was consistently associated with plasma progesterone levels greater than or equivalent to 2 ng/ml. Ovulation was evident in our investigation as the mean blood progesterone level was greater than 3 ng/ml. Therefore, it is appropriate to regard serum progesterone as a significant biochemical predictor of ovulation.

Folliclometry was also used in our investigation to look for signs of ovulation. The third treatment cycle was when maximum ovulation was shown to

have occurred; the first group had 48.8% and the second group 41% of the evidence of ovulation. However, the two groups' difference was found to be not statistically significant. The current study demonstrated that the first group total incidence of ovulation (83.3%) was substantially greater than the second group (65.9%), with a P-value of less than 0.001. In a research by Hardik Patel et al. [10], 66.4% of patients who took metformin along with clomiphene citrate experienced ovulation, in contrast to 57.12% of patients who only received clomiphene citrate. In a research by Dasari et al., [12] the group receiving both metformin and clomiphene citrate had a significantly higher ovulation rate (72%) than the group receiving clomiphene citrate alone (29%). Similar findings were found in investigations conducted by Vandermolen et al. (2001), [17] Kocak et al. (2002), [18] Batukan et al., [19] and Sturrock et al. [20], respectively. There was significant increase in ovulation rate with combined medication with clomiphene citrate and metformin as compared to clomiphene citrate alone. Results of current study were almost resembling to these studies.

In contrast, a research by Ng et al. (2001) [21] found that the group receiving metformin and clomiphene citrate (40%) had a lower ovulation rate (40%) than the control group receiving clomiphene citrate alone (70%). This outcome was inconsistent with our research. According to Moll et al. (2006) [23], there was no significant correlation seen between the addition of metformin to clomiphene citrate and an increased incidence of ovulation.

According to the current study, patients' menstrual cycles were substantially more regularized in the group treated with metformin plus clomiphene citrate (89.6%) than in the group treated with clomiphene citrate alone (38.6%) (P value=0.03). A study on the impact of metformin on irregular menstruation by Bhavana V. Sontakke et al. [22] produced results similar to this one. Given that 95% of the patients had regular cycles documented, it was discovered that metformin enabled the majority of patients to resume their menses.

The first group had a greater pregnancy rate (33.3%) than the second (20.5%), although the difference was not statistically significant (P-value=0.25). In his research, Hardik Patel et al. [10] found that patients who took metformin and clomiphene citrate together were able to conceive in 25.91% of cases, while those who used clomiphene citrate alone were only able to conceive in 23.8% of cases. In contrast to clomiphene citrate alone, patients who received combination treatment of clomiphene citrate and metformin had greater pregnancy rates (24%) according to a research by Dasari et al. [12] Pregnancy rates were greater (35%) in the group receiving combination treatment, according to Costello's review24. The pregnancy rates in these trials and our own were found to be comparable. Research by Vandermolen et al. [17] and Batukan et al. [19] showed that groups receiving combination therapy for ovulation induction had considerably greater pregnancy rates. In his research, Moll et al. (2006) [23] found no discernible variation in the pregnancy rates between the two study groups mentioned above.

In both groups, the average ovulation period lasted three months. When comparing the first cycle and sixth cycle of ovulations in the current study, the ovulation rates were higher in groups A and B, at 50% and 55.2%, respectively.

Similar findings were also noted in studies conducted by Dasari et al. [12] and Batukan et al. [19]. According to Dasari et al. study [12], the group who received combined medicine, such as metformin and clomiphene citrate, had an average ovulation length of 3.5 months. According to Batukan et al. [19], the group treated with metformin and clomiphene citrate saw an average ovulation period of 4 months.

Conclusion

Primary subfertility, which is mostly caused by anovulation or oligo ovulation, is one of the main consequences of PCOS. Two groups were given varying dosages of clomiphene citrate in the current study: one group received it in conjunction to metformin, while the other group received it just to induce ovulation.

The combination of clomiphene citrate and metformin was found to be more effective in inducing ovulation than clomiphene citrate alone.

References

1. Diamanti-Kandarakis E, Kouli CR, Bergiele AT, et al.: A survey of the polycystic ovary syndrome in the Greek island of Lesbos: hormonal and metabolic profile. J Clin Endocrinol Metab. 1999, 84:4006-4011.
2. Głuszak O, Stopińska-Głuszak U, Glinicki P, et al.: Phenotype and metabolic disorders in polycystic ovary syndrome. ISRN Endocrinol. 2012, 2012:569862.
3. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group: Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004, 19:41-47.
4. Mantzoros CS, Flier JS: Insulin resistance: the clinical spectrum. Adv Endocrinol Metab. 1995, 6:193-232.
5. Bergman RN, Prager R, Volund A, et al.: Equivalence of the insulin sensitivity index in man derived by the minimal model method

and the euglycemic glucose clamp. J Clin Invest. 1987, 79:790-800.
6. Legro RS, Castracane VD, and Kauffman RP: Detecting insulin resistance in polycystic ovary syndrome: purposes and pitfalls. Obstet Gynecol Surv. 2004, 59:141-154.
7. Antonucci T, Whitcomb R, McLain R, Lockwood D, Norris RM. Impaired glucose tolerance is normalised by treatment with the thiazolidinedione troglitazone. Diabetes Care. 1998; 20(2):188–93.
8. Palomba S, Orio F, Falbo A, Manguso F, Russo T, Cascella T, et al. Prospective parallel randomized, double-blind, doubledummy controlled clinical trial comparing clomiphene citrate and metformin as the first-line treatment for ovulation induction in nonobese anovulatory women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2005; 90(7):4068–74.
9. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene induced ovulation in the polycystic ovary syndrome. N Engl J Med. 1998338; 338(26):1876–80.
10. Patel H, Patel P, Dikshit RK, Shah S. The efficacy and safety of clomiphene citrate and metformin on ovulation induction in patients suffering from anovulatory infertility. Int J Basic Clin Pharmacol. 2015; 4:1241–6.
11. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med. 2007; 356(6):551–66.
12. 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(1):18–22.
13. Dunaif A. Molecular mechanisms of insulin resistance in polycystic ovary syndrome. Semin Reprod Endocrinol. 1994; 12:15–20.
14. Ferriman D, Gallwey JD. Clinical assessment of body hair growth in women. J Clin Endocrinol Metab. 1961; 21:1440–7.
15. Israel R, Mishell DR, Stone SC, Thorneycroft IH, Moyer DL. Single luteal phase serum progesterone assay as an indicator of ovulation. Am J Obstet Gynecol. 1972; 112(8):1043–6.
16. Nadji P, Reyniak JV, Sedlis A, Szarowski DH, Bartosik D. Endometrial dating correlated with progesterone levels. Obstet Gynecol. 1975; 45(2):193–4.
17. 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. Fertil Steril. 2001; 75(2):310–5.
18. Kocak M, Caliskan E, Simsir C, Haberal A. Metformin therapy improves ovulatory rates, cervical scores, and pregnancy rates in clomiphene citrate-resistant women with polycystic ovary syndrome. Fertil Steril. 2002; 77(1):101–6.
19. Batukan C, Baysal B. Metformin improves ovulation and pregnancy rates in patients with polycystic ovary syndrome. Arch Gynecol Obstet. 2001; 265(3):124–7.
20. Sturrock ND, Lannon B, Fay TN. Metformin does not enhance ovulation induction in clomiphene resistant polycystic ovary syndrome in clinical practice. Br J Clin Pharmacol. 2002; 53(5):469–73.
21. Ng EH, Wat NM, Ho PC. Effects of metformin on ovulation rate, hormonal and metabolic profiles in women with clomiphene-resistant polycystic ovaries: a randomized, double-blinded placebo-controlled trial. Hum Reprod. 2001; 16(8):1625–31.
22. Sontakke BV. PCOS in adolescence: effect of metformin on menstrual irregularities. Int J Reprod Contracept Obstet Gynecol. 2017; 6(8).
23. Moll E, Bossuyt P, Korevaar JC, Lambalk CB, Veen FV. Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. BMJ. 2006; 332(7556):1485.
24. Costello MF, Eden JA. A systematic review of the reproductive system effects of metformin in patients with polycystic ovary syndrome. Fertil Steril. 2003; 79(1):1–13.