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Original Research Article

Comparison of Clomiphene Citrate plus Metformin and Clomiphene Citrate Alone On Induction of Ovulation in Women with Polycystic Ovarian Syndrome: A Randomised Double Blind Clinical Study

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Abstract:

Background: The symptoms and indicators of PCOS are brought on by a prevalent metabolic and reproductive condition that affects women. Worldwide, it is thought to affect 4% of women who are childbearing age; however, in populations where the risk is higher, other sources suggest that the number is closer to 10%. The purpose of the study is to ascertain and compare, in PCOS patients, the rates of ovulation, regularization of the menstrual cycle, and pregnancy by using a combination of clomiphene citrate and metformin as well as clomiphene citrate alone.

Methods: A total of 110 patients, 55 in each group, who were diagnosed with PCOS and had primary subfertility and were between the ages of 18 to 40 were chosen between June 2023 and November 2023. Folliculometry was used to identify the main result, or the incidence of ovulation. The regularization of the menstrual cycle and the rates of pregnancy were considered secondary outcomes that were compared between the two groups.

Results: The third cycle of ovulation induction was when overall ovulation was determined to be highest, occurring in each group at 48.8% and 41%, respectively. When clomiphene citrate and metformin were given together, group A primary outcome was considerably greater (83.3%) than when clomiphene citrate was given alone (65.9%). In the group receiving metformin with CC, the secondary outcomes were much higher (89.6%). The first group had a greater pregnancy rate 33.3% than the second group (20.5%).

Conclusion: In the present study, two groups received different dosages of clomiphene citrate: one had it in combination with metformin, while the other received it only for the purpose of inducing ovulation. It was discovered that inducing ovulation in PCOS-affected women with a combination of clomiphene citrate and metformin was superior to using clomiphene citrate alone.

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

Introduction

The most common endocrinological disorder, polycystic ovarian syndrome (PCOS), affects 4%–12% of women [1]. It has been demonstrated to be the primary factor in female infertility [2]. Menstrual irregularity with concomitant anovulatory infertility and hyperandrogenism are two clinical features of PCOS [3]. It became clear over time that the disease had a broad clinical spectrum and was highly diverse. It is regarded as a syndrome rather than an illness.

Based on around 1,080 cases collected from the literature, it was revealed that approximately 69% of affected females experienced hirsutism, 74% experienced infertility, 40% were obese, slightly over 50% experienced amenorrhea, 29% experienced functional bleeding, and 12% experienced cyclical menses.

In PCOS, a strong correlation was found between testosterone and insulin levels. It was clear that IR has nothing to do with fat and is merely a common aspect of the illness. Insulin resistance is commonly defined as "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. IR is present in 50–70% of women with PCOS, and it plays a crucial part in the pathophysiology of PCOS. [4-5] It is believed that when circulating insulin levels in the body above the normal range, it leads to redundant anovulation and redundant androgen production due to the rise in circulating insulin levels in the ovary. [6]

When given to patients who are insulin resistant, insulin sensitizing medications offer promise in the treatment of PCOS. These substances work to decrease the requirement for compensatory hyperinsulinemia by increasing target tissue responsiveness to insulin. [7] They also encourage weight loss, which helps overweight PCOS patients resume their ovulatory cycles. Currently available biguanides and thiazolidinediones are insulin sensitizing drugs. Among these, ovulatory response to CC, menstrual cyclicity, and sponataneous ovulation are all increased in women with PCOS who use metformin. [8]

Because of this, it is now advised that the first line of treatment for infertile women with PCOS should be metformin, either by itself or in conjunction with clomiphene citrate. [9]

Since the ideal course of action for inducing ovulation in PCOS patients is still unknown, this study aims to clarify the function that combination therapy involving metformin and clomiphene citrate plays in this process. The purpose of this study is to evaluate the effectiveness of using metformin in addition to clomiphene citrate versus clomiphene citrate alone for inducing ovulation in PCOS patients with infertility or subfertility.

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

The randomized double blind clinical study was conducted in OPD of Department of Obstetrics and Gynaecology, Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar from June 2023 to November 2023. Women diagnosed as PCOS as suffering from primary subfertility due to anovulation, age group 18 to 40 years and who had given consent were the subjects of this study were included.

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 55 patients were placed in one group, other 55 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 were randomly assigned to 110 PCOS individuals with primary subfertility. The study involved the analysis of 48 patients from group A and 44 patients from group B, totalling 55 patients in each group.

Table 1: Distribution of cases

Group	No. of cases	Percentage
Clomiphene citrate + metformin	48	52.17%
Clomiphene citrate only	44	47.82%
Total	92	100.00%

From day three today seven of the menstrual cycle, women in Group A received ovulation induction by a single tablet of clomiphene citrate 50 mg and a tablet of metformin 500 mg twice daily.
Group B women received the same regimen as Group A for ovulation induction using a 50 mg tablet of clomiphene citrate only. (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	15(31.3%)	13(29.5%)	0.16
25-32	27(56.3%)	21(47.7%)	
33-38	6(12.5%)	10(22.7%)	

When the age distribution of the patients was examined, the highest number of patients were found to be 25–32 years old, followed in descending order by 17–24 years old and 33–38 years old (Table 2).
Between the two groups, there was no statistically significant difference.

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	39(81.3%)	33(75.0%)	
Regular	9(18.8%)	11(25.0%)	

The majority of the patients in this study had irregular menstrual cycles, it was found. Regarding the menstrual histories of the two groups, there was no statistically significant difference. (Table 3)

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

	Groups		
	Clomiphene citrate + metformin (n=48)	**Clomiphene citrate only (n=44)**	**p-value (t-test)**
BMI (Normal/overweight/ obese) [Mean±SD]	28.66±3.89	28.0±4.18	
	No. (%)	**N(%)**	0.43
Normal (18.5-24.9)	6(12.5%)	10(22.7%)	
Overweight (25-29.9)	20(41.7%)	18(40.9%)	
Obese (>30)	22(45.8%)	16(36.4%)	

The highest number of patients were clearly 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), and finally, with a normal BMI (12.5% in the first group, 22.7% in the second group). For the two groups, no statistical significance was found. (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	17(35.4%)	27(61.4%)	
Normal	31(64.6%)	17(38.6%)	

A 75-gram glucose oral glucose tolerance test was administered to the patients in both groups. The incidence of abnormal OGTT (61.4%) was found to be significantly greater in the second group (CC alone) than in the first group (35.4%).
(P-value less than 0.05) (Table 5).

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 patients in this study were primarily between the ages of 25 and 32. Of them, 56.3% belonged to group A and 47.7% to group B. The means for each group were 25.23±4.01 and 26.57±4.62, respectively. The age of the patients in the two groups did not differ in a way that was statistically significant (P-value = 0.16). The mean age distribution in the Hardik Patel et al., [10] study was 26.04±7.78, which was comparable to our research.

Merely 8.33% of the population was older than 31. Legro et al. study11 produced similar findings, with a mean age distribution of 27.9±4.The majority of patients in the first and second groups in this study, 64.6% and 65.9%, respectively, came from rural areas.While comparable between the two groups, other characteristics such as menstruation history and socioeconomic level were not statistically significant. In our study, the majority of patients had obesity BMI of 48.5% in the first group and 36.4% in the second, with mean values of 28.66±3.89 and 28±4.18, respectively. BMI < 25 kg/m2 was observed in 12.5% and 22.7% of the aforementioned groups, respectively.

Twenty patients (41.67%) had a body mass index (BMI) of less than 25 kg/m2, while 28 patients (58.33%) had a BMI of more than 25 kg/m2, according to the study done by Hardik Patel et al. [10] Papa Dasari et al. [12] study revealed that obesity was present in 37.5% of the patients, which is close to and nearly identical to our findings. While Dunaif et al. [13] study revealed a greater incidence of obesity (55.87%) and (65%) in the relevant order of medication when compared to our study, Moll et al. conducted some similar investigations. In the current study, it was discovered that 18.8% of patients in Group A and 18.2% of patients in Group B had symptoms similar to acne. The Ferriman Gallway Scale [14] indicated that hirsutism was present in 38.3% of patients on average in both groups, however the differences were not statistically significant.

In a research by Hardik Patel et al., exactly 56.25% of patients had hirsutism, while 45.83% of patients had acne. [10] According to a study by Papa Dasari et al. [12], hirsutism was found in 85% of participants. Compared to our study, these investigations found a higher frequency of hirsutism in PCOS patients. While a lipid profile, liver function test, and USG of the entire abdomen were performed as part of our study, no statistically significant differences were seen between the two groups. In our study, we measured fasting blood sugar (mg/ml) and performed an oral glucose tolerance test. 48.4% of patients in both groups were determined to be deranged on average. FBS and OGTT differences between the two groups were both statistically significant (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. In a similar vein, Nadji et al. [16] discovered that plasma progesterone levels greater than or equal to 2 ng/ml were consistently linked to secretory endometrium, which in turn indicated ovulation. In our study as mean serum progesterone was > 3ng/ml, there was an evidence of ovulation. Hence, the serum progesterone deserves to be considered, an important 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] andSturrock 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 almost resembled 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 review [24]. 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

One of the main side effects of PCOS is primary subfertility, which is primarily brought on by anovulation or oligo ovulation. In the current study, two groups received different doses of clomiphene citrate: one received it in addition to metformin, while the other received it only for the purpose of inducing ovulation. When compared to clomiphene citrate alone, it was discovered that the combination of clomiphene citrate and metformin was more efficient in inducing ovulation.

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