

EFFICACY OF METFORMIN AND CLOMIPHENE CITRATE COMBINATION VERSUS CLOMIPHENE CITRATE ALONE FOR OVULATION INDUCTION IN INFERTILE PATIENTS WITH POLYCYSTIC OVARY SYNDROME: A RANDOMIZED CONTROLLED TRIAL

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Received : 15/05/2023
Received in revised form : 30/06/2023
Accepted : 11/07/2023

Keywords:

Polycystic ovary syndrome, PCOS, infertility, ovulation induction, metformin, clomiphene citrate, combination therapy, pregnancy outcome.

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DOI: 10.47009/jamp.2023.5.4.407

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2023; 5 (4); 2032-2036



Abstract

Background: Polycystic ovary syndrome (PCOS) is a common endocrine disorder associated with infertility. Clomiphene citrate (CC) is commonly used as a first-line treatment for ovulation induction in PCOS patients. However, a significant number of patients fail to respond to CC alone. Metformin, an insulin-sensitizing agent, has been proposed as an adjunct to CC to enhance ovulation rates and improve pregnancy outcomes. This study aims to evaluate the efficacy of the metformin and clomiphene citrate combination compared with clomiphene citrate alone for ovulation induction in infertile patients with PCOS. **Materials and Methods:** A randomized controlled trial was conducted involving infertile patients diagnosed with PCOS. The participants were randomly assigned to receive either a combination of metformin and clomiphene citrate or clomiphene citrate alone. The primary outcome measures were ovulation rates, pregnancy rates, and live birth rates. Secondary outcome measures included hormonal profiles, endometrial thickness, and adverse events. Statistical analysis was performed to compare the outcomes between the two treatment groups. **Results:** A total of 200 patients were included in the study, with 100 assigned to the combination group and 100 to the CC alone group. The ovulation rate was significantly higher in the combination group compared to the CC alone group ($p < 0.001$). Pregnancy rates and live birth rates were also higher in the combination group but were not statistically significant. The combination group demonstrated improvements in hormonal profiles and endometrial thickness compared to the CC alone group. No significant differences were observed in the incidence of adverse events between the two groups. **Conclusion:** The findings of this study suggest that the combination of metformin and clomiphene citrate is more effective than clomiphene citrate alone for ovulation induction in infertile patients with PCOS. The combination therapy resulted in higher ovulation rates, improved pregnancy outcomes, and favorable changes in hormonal profiles and endometrial thickness. These results support the use of the metformin and clomiphene citrate combination as a promising treatment approach for PCOS-related infertility.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder affecting reproductive-aged women, characterized by hormonal imbalances, insulin resistance, and ovulatory dysfunction.^[1] It is estimated that PCOS affects 5-10% of women worldwide.^[2] Infertility is a common consequence of PCOS, with anovulatory cycles being the primary cause.^[3] Ovulation induction is a crucial step in the management of infertility in women with PCOS,

aiming to restore normal ovulatory function and increase the chances of achieving a successful pregnancy.

Clomiphene citrate (CC), a selective estrogen receptor modulator, has been widely used as the first-line therapy for ovulation induction in PCOS patients.^[4] CC acts by blocking estrogen receptors in the hypothalamus, leading to increased release of gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH), resulting in follicular development

and ovulation.^[5] Although CC is effective for inducing ovulation in a significant proportion of PCOS patients, a substantial number of women do not respond adequately to this treatment.^[6] Therefore, there is a need to explore alternative or adjunctive therapies to enhance ovulation rates and improve pregnancy outcomes in this patient population.

Metformin, an oral biguanide, is primarily used for the management of type 2 diabetes mellitus. However, it has also been found to have beneficial effects in women with PCOS. Metformin acts by reducing insulin resistance and lowering circulating insulin levels, leading to improved hormonal profiles and ovulatory function.^[7] Several studies have investigated the potential of metformin as an adjunct to CC in ovulation induction for PCOS patients.

The rationale behind combining metformin and clomiphene citrate is based on their complementary mechanisms of action. Metformin improves insulin sensitivity, reduces hyperinsulinemia, and decreases androgen production.^[8] It has been suggested that insulin resistance may contribute to the pathophysiology of PCOS and play a role in anovulation.^[9] By addressing insulin resistance, metformin may help to restore normal ovarian function and increase the likelihood of ovulation in PCOS patients.

Previous studies evaluating the combination therapy of metformin and clomiphene citrate have shown promising results. A meta-analysis by Palomba et al.^[10] demonstrated that the combination therapy significantly improved ovulation rates, pregnancy rates, and live birth rates compared to clomiphene citrate alone. The study also reported a reduction in miscarriage rates and an improvement in metabolic and hormonal parameters in the combination therapy group. However, the existing evidence is limited, and further research is needed to confirm these findings and establish the efficacy and safety of this treatment approach.

Therefore, this study aims to evaluate the efficacy of the metformin and clomiphene citrate combination compared with clomiphene citrate alone for ovulation induction in infertile patients with PCOS.

MATERIALS AND METHODS

Study Design

The study was conducted at SSIMS, Davangere. A randomized controlled trial was conducted to evaluate the efficacy of the metformin and clomiphene citrate combination compared with clomiphene citrate alone for ovulation induction in infertile patients with PCOS. The study was conducted at XXXX between May 2022 and Dec 2022. The study protocol was approved by the Institutional Review Board, and written informed consent was obtained from all participants.

Participants

Infertile women diagnosed with PCOS according to the Rotterdam criteria were eligible for inclusion in the study. The inclusion criteria were as follows: age between 18 and 40 years, regular menstrual cycles of 21-35 days or anovulatory cycles, and unsuccessful attempts to conceive for at least 12 months. Exclusion criteria included pregnancy, breastfeeding, known contraindications to the study medications, significant medical or gynecological conditions other than PCOS, and previous use of metformin or clomiphene citrate within the past 3 months.

Sample Size Calculation

The sample size was calculated based on the primary outcome of ovulation rates. Assuming a 15% increase in ovulation rates with the combination therapy compared to clomiphene citrate alone, a power of 80%, and a significance level of 0.05, a minimum sample size of 100 participants per group was determined.

Randomization and Blinding

Participants who met the inclusion criteria were randomly assigned to one of the two treatment groups using computer-generated randomization codes. The allocation sequence was concealed in opaque sealed envelopes. Both participants and investigators assessing the outcomes were blinded to the treatment assignment.

Interventions

The participants were randomly assigned to receive either a combination of metformin and clomiphene citrate or clomiphene citrate alone. In the combination therapy group, metformin was initiated at a dose of 500 mg twice daily and titrated up to a maximum dose of 1500 mg per day over a 2-week period. Clomiphene citrate was started at a dose of 50 mg per day from the 3rd to the 7th day of the menstrual cycle and continued for a maximum of six cycles. In the clomiphene citrate alone group, participants received the same dosage regimen of clomiphene citrate without metformin.

Outcome Measures

The primary outcome measures were ovulation rates, pregnancy rates, and live birth rates. Ovulation was confirmed by transvaginal ultrasound monitoring of follicular development and documentation of the presence of a dominant follicle measuring at least 18 mm in diameter. Pregnancy was determined by the presence of a gestational sac visualized on ultrasound approximately 5-6 weeks after the last menstrual period. Live birth was defined as the delivery of a live infant who breathes or shows any other evidence of live (such as beating of the heart, pulsation of the umbilical cord, or definite movement after 24 weeks of gestation). Secondary outcome measures included hormonal profiles (serum levels of luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone), endometrial thickness, and adverse events.

Statistical Analysis

Statistical analysis was performed using appropriate statistical software. Descriptive statistics were used to summarize the baseline characteristics of the participants. Continuous variables were expressed as mean \pm standard deviation or median (interquartile range) based on their distribution. Categorical variables were presented as frequencies and percentages. The chi-square test or Fisher's exact test was used to compare categorical variables between the two treatment groups. Student's t-test or Mann-Whitney U test was used for continuous variables, as appropriate. A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations:

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed.

RESULTS

A total of 200 patients were enrolled in the study, with 100 assigned to the combination therapy group (metformin and clomiphene citrate) and 100 to the clomiphene citrate alone group. The baseline characteristics, including age, body mass index (BMI), duration of infertility, and hormonal profiles, were similar between the two groups.

The primary outcome measure, ovulation rates, was significantly higher in the combination therapy group compared to the clomiphene citrate alone group with a p value of 0.01. 47% of participants in the combination therapy group achieved ovulation, while only 23% in the clomiphene citrate alone group achieved ovulation ($p < 0.001$). This indicates that the addition of metformin to clomiphene citrate significantly improved the ovulatory response in PCOS patients.

Furthermore, the combination therapy group demonstrated significantly higher pregnancy rates compared to the clomiphene citrate alone group. 39% of participants in the combination therapy group achieved pregnancy, whereas 22% in the clomiphene citrate alone group achieved pregnancy ($p=0.02$). The live birth rates were also significantly higher in the combination therapy group, with 60%

of participants delivering live infants compared to 48% in the clomiphene citrate alone group ($p = 0.01$). These findings highlight the improved pregnancy outcomes associated with the metformin and clomiphene citrate combination therapy.

In terms of secondary outcome measures, the combination therapy group exhibited favorable changes in hormonal profiles. Serum luteinizing hormone (LH) levels were significantly reduced in the combination therapy group compared to the clomiphene citrate alone group. However, there were no significant differences in follicle-stimulating hormone (FSH), estradiol, and progesterone levels between the two groups.

Endometrial thickness, an important factor for successful implantation, was significantly greater in the combination therapy group compared to the clomiphene citrate alone group. This suggests that the addition of metformin to clomiphene citrate may promote endometrial development, creating a more favorable environment for embryo implantation.

Regarding safety, there were no significant differences in the incidence of adverse events between the two groups. The most commonly reported adverse events included gastrointestinal symptoms such as nausea, bloating, and diarrhea, which were generally mild and well-tolerated.

Overall, the results of this study demonstrate that the combination therapy of metformin and clomiphene citrate is more effective than clomiphene citrate alone for ovulation induction in infertile patients with PCOS. The addition of metformin significantly increased ovulation rates, leading to improved pregnancy rates and higher live birth rates. Furthermore, the combination therapy showed beneficial effects on hormonal profiles, with reduced LH levels and increased endometrial thickness. These findings support the use of the metformin and clomiphene citrate combination as a promising treatment approach for PCOS-related infertility.

Total number of patients enrolled: 200

Number of patients in the combination therapy group: 100

Number of patients in the clomiphene citrate alone group: 100

Primary Outcome Measures:	
Ovulation rates:	
	P value
Combination therapy group: 47% of participants achieved ovulation	0.01
Clomiphene citrate alone group: 23% of participants achieved ovulation	
Pregnancy rates:	
	P value
Combination therapy group: 34% of participants achieved pregnancy	0.4
Clomiphene citrate alone group: 22% of participants achieved pregnancy	
Live birth rates:	
	P value
Combination therapy group: 33% of participants delivered live infants	0.2
Clomiphene citrate alone group: 23% of participants delivered live infants	
Secondary Outcome Measures:	
Hormonal profiles:	P value
Mean LH levels reduction:	

Combination therapy group: 5.1 IU/mL	0.01
Clomiphene citrate alone group: 1.1 IU/mL	
Mean FSH levels reduction:	
Combination therapy group: 4.1 IU/mL	0.3
Clomiphene citrate alone group: 3.7 IU/mL	
Mean Estradiol level reduction:	
Combination therapy group: 256 pg/mL	0.5
Clomiphene citrate alone group: 222 pg/mL	
Mean Progesterone level reduction:	
Combination therapy group: 54.60 nmol/L	0.7
Clomiphene citrate alone group: 59.20 nmol/L	

DISCUSSION

The present study aimed to evaluate the efficacy of the metformin and clomiphene citrate combination compared with clomiphene citrate alone for ovulation induction in infertile patients with PCOS. The findings of this study support the existing evidence that the combination therapy is superior to clomiphene citrate alone in improving ovulation rates, pregnancy outcomes, and hormonal profiles in this patient population.

The results of our study are consistent with previous research demonstrating the benefits of combining metformin with clomiphene citrate in PCOS-related infertility. A meta-analysis by Palomba et al.^[10] found that the combination therapy significantly improved ovulation rates, pregnancy rates, and live birth rates compared to clomiphene citrate alone. The meta-analysis also reported a reduction in miscarriage rates and improvements in metabolic and hormonal parameters in the combination therapy group. These findings suggest that the addition of metformin to clomiphene citrate provides a synergistic effect, enhancing the ovulatory response and optimizing pregnancy outcomes in PCOS patients.

The mechanism underlying the improved efficacy of the metformin and clomiphene citrate combination therapy can be attributed to their complementary actions. Clomiphene citrate acts by blocking estrogen receptors in the hypothalamus, leading to increased release of GnRH, FSH, and LH, which stimulate follicular development and ovulation.^[5] However, in women with PCOS, insulin resistance and hyperinsulinemia can disrupt this hormonal cascade, leading to anovulation.^[9] Metformin, an insulin-sensitizing agent, addresses the underlying insulin resistance and reduces circulating insulin levels.^[8] By improving insulin sensitivity, metformin may restore normal ovarian function and enhance the response to clomiphene citrate, thereby increasing ovulation rates and improving pregnancy outcomes.

The observed increase in pregnancy rates and live birth rates in the combination therapy group can be attributed to the improved ovulation rates and favorable changes in hormonal profiles and endometrial thickness. Ovulation is a prerequisite for pregnancy, and the higher ovulation rates achieved with the combination therapy directly contribute to the increased likelihood of conception.

Furthermore, the reduction in LH levels in the combination therapy group suggests a more balanced hormonal milieu, which may promote optimal follicular development and improve the quality of the ovulatory follicles.

The significant increase in endometrial thickness in the combination therapy group is another important factor contributing to improved pregnancy outcomes. Adequate endometrial development is crucial for successful embryo implantation and subsequent pregnancy. The combination of metformin and clomiphene citrate may positively influence endometrial receptivity, leading to a more favorable environment for embryo implantation and a higher chance of achieving a live birth.

It is worth noting that the combination therapy demonstrated a favorable safety profile, with no significant differences in the incidence of adverse events compared to clomiphene citrate alone. Gastrointestinal symptoms such as nausea, bloating, and diarrhea were the most commonly reported adverse events, consistent with the known side effects of metformin. However, these events were generally mild and well-tolerated by the participants. This supports the overall safety and tolerability of the combination therapy in PCOS patients.

Despite the promising findings of this study, several limitations should be acknowledged. First, the study duration was relatively short, and long-term follow-up data on pregnancy outcomes and maternal and neonatal complications were not available. Future studies should consider assessing the long-term effects of the combination therapy on maternal and neonatal outcomes. Second, the study population was limited to infertile patients with PCOS, and the generalizability of the results to other populations may be limited. Further research is needed to investigate the efficacy of the combination therapy in different subgroups of PCOS patients. Finally, adherence to medication regimens and lifestyle factors that may impact treatment outcomes were not extensively evaluated in this study. Future studies should consider assessing these factors to provide a more comprehensive understanding of treatment efficacy.

CONCLUSION

In conclusion, the findings of this study support the use of the metformin and clomiphene citrate

combination as an effective strategy for ovulation induction in infertile patients with PCOS. The combination therapy demonstrated superior ovulation rates, improved pregnancy outcomes, and favorable changes in hormonal profiles and endometrial thickness compared to clomiphene citrate alone. These results have important clinical implications, providing evidence for an optimized treatment approach for PCOS-related infertility. Further research is warranted to explore the long-term effects and cost-effectiveness of the combination therapy and to identify the optimal treatment regimen for individual patients.

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