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OUTCOME OF OVULATION INDUCTION WITH CLOMIPHENE CITRATE VERSUS COMBINED CLOMIPHENE CITRATE AND METFORMIN AT SAAD ABU ELELLA UNIVERSITY HOSPITAL

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Abstract
Background: Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among women of reproductive age. Although Clomiphene Citrate (CC) is an available standard ovulation induction treatment, combination therapy with Metformin will be more effective in treating insulin-resistant cases. Nevertheless, the effects of this combination on ovulation and pregnancy success are unknown.
Objective: To assess whether the addition of Metformin to CC in women with PCOS improves ovulation rate.
Methods: This prospective clinical trial included 81 women with PCOS-related infertility which was defined according to the Rotterdam criteria. Two groups, CC alone (n=42) or CC and Metformin (n=39), were assigned. Ovulation rates, follicular development and pregnancy outcomes were assessed by transvaginal ultrasound and relevant hormonal tests.
Results: The CC plus Metformin group showed significantly higher ovulation rates (79.5% vs. 54.8%, p=0.018) and pregnancy rates (30.8% vs. 9.5%, p=0.016) compared to the CC-only group. No cases of ovarian hyperstimulation were observed.
Conclusion: For Sudanese women with PCOS, combining metformin with CC could significantly improve their chances of ovulation and pregnancy. This approach may offer a valuable first-line treatment option, especially in regions where advanced fertility treatments are limited.
Keywords: PCOS, Clomiphene Citrate, Metformin, Ovulation Induction, Infertility.

Introduction

Polycystic ovary syndrome (PCOS) affects women worldwide, with prevalence estimates ranging from 4% to 12%. In Sudan, where our study took place, PCOS is a leading cause of infertility, characterized by hormonal imbalances, irregular menstruation, and difficulty conceiving [1, 2].

Clomiphene citrate (CC) has been the go-to medication for inducing ovulation in PCOS patients for decades [3]. However, its success rate is far from perfect – roughly 15% to 40% of women fail to ovulate with CC alone. This gap in treatment efficacy led our team to explore whether adding metformin, a drug that improves insulin sensitivity, could enhance outcomes [4].

While numerous studies have examined the combination of Metformin and CC, results have been inconsistent due to variations in study design and participant characteristics. Our study aims to contribute to this body of research by assessing the efficacy of adding Metformin to CC for ovulation induction in Sudanese women with PCOS.

Material and method

Study Design and Participants

We conducted a non-randomized prospective clinical trial at the University of Khartoum Fertility Centre, Saad Abu Elella Hospital, Sudan, from April 2016 to July 2017. Women aged 18 to 45 with PCOS, diagnosed according to Rotterdam criteria [5], were eligible for participation. We excluded women with other causes of infertility and those with male factor infertility.

Ethical Considerations

Our study adhered to international ethical guidelines for biomedical research. We obtained approval from the Research Committee of the Sudan Medical Specialization Board and Saad Abu Elella Hospital management. All participants provided informed written consent, and we maintained patient confidentiality throughout the study.

Intervention

Participants were allocated to two treatment arms:

1. CC alone (Arm A): 100 mg (50 mg twice daily) from day 2-6 of the menstrual cycle.

2. CC plus metformin (Arm B): CC as in Arm A, plus metformin 500 mg three times daily continuously.

Follicular growth was monitored by transvaginal ultrasound from day 7 of the menstrual cycle until a dominant follicle reached 18-20 mm. At this point, 10,000 IU of human chorionic gonadotropin (hCG) was administered intramuscularly, and patients were advised to have intercourse 36 hours later. Ovulation was confirmed by transvaginal ultrasound 48 hours after hCG administration.

Outcome Measures

Our study focused on two critical measures of fertility treatment success: ovulation rates and pregnancy rates. Secondary outcomes included the number of follicles, number of mature follicles, and days of stimulation.

Statistical Analysis

We analyzed our data using IBM SPSS Statistics 20. For continuous variables, we applied Student's t-tests or Mann-Whitney U tests as appropriate. Categorical outcomes were assessed using chi-square or Fisher's exact tests. We set significance at $p < 0.05$ for all two-tailed tests. Effect sizes were calculated using Cohen's d or Cramer's V. To account for potential confounders, we conducted subgroup analyses by BMI and age. Throughout, we adhered to SAMPL guidelines for biomedical statistical reporting.

Results

Baseline Characteristics

The study involved 81 women aged 17 to 40 years (CC alone: n=42; CC plus metformin: n=39). The baseline characteristics, such as age, body mass index (BMI), and hormonal levels (FSH, LH, and prolactin), were similar between the two groups, with no significant differences observed (Table 1).

Table 1. Baseline Characteristics of Study Participants

Characteristic	CC alone (n=42)	CC + Metformin (n=39)	P-value
Age (years)	28.50 ± 5.63	28.51 ± 5.72	0.991
BMI (kg/m²)	26.6 ± 3.8	27.4 ± 4.1	0.339
FSH (mIU/mL)	8.0 ± 3.2	7.8 ± 3.1	0.814
LH (mIU/mL)	9.3 ± 4.1	9.3 ± 4.0	0.920
Prolactin (ng/mL)	43.2 ± 29.7	74.2 ± 156.3	0.226
BMI Distribution			0.322
○ <25 kg/m²	15 (35.7%)	15 (38.5%)	
○ 25-29.9 kg/m²	20 (47.6%)	13 (33.3%)	
○ ≥30 kg/m²	7 (16.7%)	11 (28.2%)	

Data presented as mean ± SD or n (%). BMI: Body Mass Index; FSH: Follicle-Stimulating Hormone; LH: Luteinizing Hormone.

Ovulation and Pregnancy Rates

The CC plus metformin group demonstrated significantly higher ovulation rates than CC alone (79.5% vs. 54.8%, p=0.018). Similarly, pregnancy rates were superior in the combination therapy group (30.8% vs. 9.5%, p=0.016) (Table 2).

Table 2. Ovulation and Pregnancy Rates

Outcome	CC alone (n=42)	CC + Metformin (n=39)	P-value
Ovulation	23 (54.8%)	31 (79.5%)	0.018
No ovulation	19 (45.2%)	8 (20.5%)	
Pregnancy	4 (9.5%)	12 (30.8%)	0.016
No pregnancy	38 (90.5%)	27 (69.2%)	

Data presented as n (%).

Follicular Development and Stimulation Duration

There were no significant differences between the two groups in terms of the number of follicles, number of mature follicles, or days of stimulation (Table 3).

Table 3. Follicular Development and Stimulation Duration

Parameter	CC alone (n=42)	CC + Metformin (n=39)	P-value
Number of follicles	2.95 ± 2.72	3.15 ± 2.28	0.720
Number of mature follicles	1.26 ± 1.40	1.49 ± 1.23	0.445
Days of stimulation	9.14 ± 3.38	10.03 ± 2.93	0.215

Data presented as mean ± SD.

Discussion

This study shows that combining metformin with CC notably enhances ovulation and pregnancy rates in women with PCOS undergoing ovulation induction. These findings are consistent with several previous studies, including those by Ayaz et al. [6] and Leanza et al. [7], which reported similar improvements in ovulation and pregnancy rates with combination therapy.

The increased effectiveness of the CC and metformin combination could be linked to metformin's insulin-sensitizing effects [8]. By enhancing insulin sensitivity, metformin may lower hyperandrogenism and balance hormonal levels, creating a more conducive environment for follicular growth and ovulation [9]. Additionally, Metformin might directly influence ovarian steroidogenesis and folliculogenesis [10, 11].

Interestingly, we found no significant differences in the number of total or mature follicles between the two groups. This suggests that the improved ovulation and pregnancy rates with combination therapy may result from mechanisms beyond increased follicular recruitment, such as enhanced oocyte quality, improved endometrial receptivity, or reduced systemic inflammation [12, 13]. These results contrast with those of Ben Ayed et al., who observed a higher number of mature follicles in the CC+Metformin group compared to the CC+placebo group [14].

The absence of a difference in stimulation duration between the groups is noteworthy, indicating that adding Metformin does not prolong the treatment cycle. This is an important consideration for both patients and clinicians.

Our findings add to the growing evidence supporting metformin as an adjunct to CC in women with PCOS. However, it is essential to recognize that not all studies have demonstrated positive outcomes with this combination therapy [15, 16]. This heterogeneity in outcomes may be due to differences in study populations, dosing regimens, or duration of treatment. Future research should aim to identify specific subgroups of PCOS patients who are most likely to benefit from combination therapy, possibly by stratifying patients based on factors such as insulin resistance or BMI.

Strengths of our study include its prospective design, relatively large sample size, and the use of standardized protocols for ovulation induction and monitoring. Limitations include the non-randomized allocation of participants and the lack of long-term follow-up to assess live birth rates and potential adverse effects.

Conclusion

The addition of metformin to CC significantly improves ovulation and pregnancy rates in women with PCOS undergoing ovulation induction. This combination therapy may be considered as a first-line treatment option for this patient population, particularly in settings where more advanced fertility treatments are not readily available or affordable. Future research should focus on identifying optimal dosing regimens, treatment duration, and patient characteristics that predict the best response to combination therapy.

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