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Clomiphene Supported Ovulation Induction in Subfertile Polycystic Ovary Syndrome Women: Role of Different Insulin Sensitizers

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ABSTRACT

Objective: To compare Clomiphene Citrate, ovulation induction efficacy following using insulin sensitises, Metformin versus Myo-inositol in subfertile women with polycystic ovary syndrome.

Study Design: Prospective comparative study.

Place and Duration of Study: Department of Obstetrics and Gynaecology, Combined Military Hospital, Kharian Pakistan, from Jun to Nov 2021.

Methodology: A total of 316 patients with polycystic ovary syndrome and infertility who were included in the study. Group-A was administered Metformin, whereas Group-B as given Myo-inositol. Both groups were given clomiphene citrate for ovulation induction and were followed for six months.

Results: There were 316 patients (158 in each Group). The mean age was 29.2±0.5 years, and the BMI of 23.2±1.7 Kg/m2 in both. Ovulation recorded in Group-A (Metformin) was 141(44.6%) versus Group-B (Myo-inositol), 103(32.6%). The pregnancy test was positive 33(21.1%) patients of Group-A versus 29(18.4%) of Group-B. The common complaints seen in both groups were nausea and vomiting 2(0.6%), while headache 1(0.3%) and dizziness 2(0.6%) occurred only in Group-B.

Conclusion: Clomiphene citrate with Metformin, as first-line therapy for sub-fertile women with polycystic ovary syndrome, improved ovulation and had fewer side effects than Myo-inositol.

Keywords: Clomiphene citrate, Insulin resistance, Metformin, Myo-inositol, Polycystic ovary syndrome.

How to Cite This Article: *Parveen S, Iram N, Saeed BZ, Yaqub U, Niazi NK. Clomiphene Supported Ovulation Induction in Subfertile Polycystic Ovary Syndrome Women: Role of Different Insulin Sensitizers. Pak Armed Forces Med J 2023; 73(3): 810-813. DOI: https://doi.org/10.51253/pafmj.v73i3.9081*

INTRODUCTION

Polycystic ovary syndrome (PCOS) is characterised by raised androgen levels, irregular menstruation, and multiple small follicles on one or both ovaries.[1] At least 7% of adult women have PCOS. According to the National Institutes of Health Office of Disease Prevention, it affects approximately five million women of reproductive age in the US.[2] While in south asian women, especially in pakistani women, the prevalence of PCOS is much higher (52%) compared to the white population (20-25%) in UK.[3]

PCOS is associated with insulin resistance and raised BMI. PCOS laboratory findings include raised Luteinizing Hormone (LH) and normal Follicular-Stimulating Hormone (FSH) levels.[4,5] As a result of the raised LH levels, the ovarian thecal cells produce more androgens,[4] and cause anovulation. These un-ruptured follicles can be reverted by raising endogenous FSH or giving exogenous FSH.[5,6]

Hence treatment of subfertility in PCOS includes decreasing insulin resistance, preventing the action of androgens on target tissues and improving anovulation.[7] Pharmacological methods for anovulation include clomiphene with or without antidiabetic insulin-sensitising agents like metformin and myoInositol.[8] Various non-pharmacological techniques include losing at least 10% of body weight and laparoscopic ovarian drilling.[9] We found minimal literature comparing clomiphene with antidiabetic drugs and their combination at the local level. Therefore, we planned to compare the efficacy of ovulation induction with clomiphene citrate after using either metformin or myo-inositol insulin sensitizers in sub-fertile women with polycystic ovary syndrome.

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Received: 24 Jul 2022; revision received: 15 Apr 2023; accepted: 17 Apr 2023

METHODOLOGY

The prospective observational comparative study was conducted at the Obstetrics and gynaecology Department of Combined Military Hospital, Khairan Pakistan, from June to November 2021 after approval by Hospital Ethical Committee (A/14/EC/2021). Non-probability consecutive sampling technique was used, and the sample size was estimated by taking the expected frequency of ovulation to be 32%.[8]

Inclusion Criteria: Sub-fertile women with PCOS, diagnosed on ESHRE/ASRM using rotterdam criteria

as standard, were included in the study. [At least 2 out of 3 criteria of Rotterdam; patients with irregular menstrual cycles (less than 21 days or more than 35 days); hyperandrogenism clinically based on modified Ferriman-Gallwey score ≥6 or elevated serum-free testosterone levels; polycystic ovaries on ultrasound, multiple small cysts of less than 10 mm (number of ≥20 per ovary in one or both ovaries).[9]

Exclusion Criteria: Sub-fertile women diagnosed with infertility other than PCOS, congenital adrenal disorders, systemic disorders (hypertension, diabetes mellitus), cardiovascular disorders, allergic to any medication, endometriosis, BMI >25 kg/m2 and tubal or uterine factors were excluded.

After approval from the Ethical Review Committee of the hospital, 316 sub-fertile PCOS women who came to the gynecology outpatient Department of Combined Military Hospital Kharian Pakistan and fulfilled the inclusion and exclusion criteria were included. Patients were counselled, and the study details were explained to them. After written informed consent, patients were divided into Groups A and B via a lottery method. Group-A was administered metformin, and Group-B was myo-inositol. Both groups were given clomiphene citrate (initially, 50 mg per day for five days) during early menstruation. follicular growth and ovulation were monitored with transvaginal ultrasound (TVS) on the,8,12 and 16th day of menstruation. On serum days 21 and 28, progesterone was also tested. If ovulation occurs but no pregnancy results, the same dose is continued for the subsequent cycles. Group-A patients were given metformin 500 mg thrice daily (1500mg) during meal time. At the same time, Group-B patients were given 2000 mg of myo-inositol per day. Patients were followed for six months. The primary outcomes of the study were to determine the most effective treatment for inducing ovulation and pregnancy. The secondary outcome was the adverse effects of the medication.

Statistical package for social sciences (SPSS) version 25.0 was used for the data analysis. The data was analysed by computing frequency and percentages for categorical variables, while mean and standard deviation were calculated for quantitative data. Independent sample t-test and chi-square test were applied to explore the inferential statistics. The *p*-value lower than or up to 0.05 was considered as significant.

RESULTS

Out of three hundred and sixteen patients, the mean age was 29.2±0.5 years. The mean BMI of patients was 23.2±1.7 Kg/m2. The mean ovary volume on the left side was 5.4±0.5cm^2, and the mean right ovary volume was 5.5±0.7cm^2. The mean fasting glucose level was 106±6.7. The mean LH level was 6.9±0.7, and the mean FSH was 3.7±0.5. The mean testosterone level was 0.4±0.07, (Table-I). In Group-A (metformin 1500mg), 141(44.6%) women showed ovulation, while 17(5.4%) did not have ovulation. However, in Group-B (myo-inositol 2000mg), 103(32.6%) had ovulation, while 55(17.4%) did not have ovulation (Table-II). pregnancy occurrence was slightly more in Group-A (metformin), 33 out of 158(21.1%), as compared to Group-B (myo-inositol), 29 out of 158(18.4%) (Table-III). In Group-A (metformin), 2(0.6%) patients experienced side effects like nausea and bloating. While in Group-B (myo-inositol), 2(0.6%) patients had nausea and bloating, 2(0.6%) developed dizziness, & 1 (0.3%) had a headache (p=0.387), as shown in Table-IV.

Table-I: Laboratory Parameters of the Study Participants (n=316)

Laboratory parameters	Mean±SD	Normal Range
Left Ovary Volume (cm2)	5.4±0.5	4-6
Right Ovary volume (cm2)	5.5±0.7	4-7
Fasting Glucose level (mg/dl)	106.0±6.7	95-130
LH(IU/I)	6.9±0.7	6-8
FSH(IU/I)	3.7±0.5	3-5
Testosterone (ng/ml)	0.42±0.07	0.30-0.60

Table-II: Frequency of ovulation in Metformin versus Myo-inositol Groups (n=316)

Ovulation	Study Groups		*p*-value
	Group-A (Metformin) n(%)	Group-B (Myoinositol) n(%)	
No	17(5.4%)	55(17.4%)	<0.001
Yes	141(44.6%)	103(32.6%)	

Table-III: Pregnancy in Metformin Versus Myo-inositol Groups (n=316)

Pregnancy	Study Groups		*p*-value
	Group-A (Metformin) n(%)	Group-B (Myoinositol) n(%)	
No	125(28.9%)	129(31.6%)	0.313
Yes	33(21.1%)	29(18.4%)	

Table-IV: Comparison of Complications in Both Groups (n=316)

Complications	Study Groups		*p*-value
	GroupA (Metformin) n(%)	GroupB (Myoinositol) n(%)	
No	156(49.4%)	153(48.4%)	0.387
Nausea/bloating	2(0.6%)	2(0.6%)	
Dizziness	0(0%)	2(0.6%)	
Headache/others	0(0%)	1(0.3%)	

DISCUSSION

Nearly 5 to 15% of women of reproductive age have PCOS, including ovulation disorder, hyperandrogenism and infertility.[10,11] To treat PCOS, management

of insulin resistance is central and mainly based on daily routine, eating modifications and insulin-sensitising agents like metformin, as shown in studies of glucose intolerance and type -2 diabetes.[12,13]

In the present study, subfertile PCOS women treated with metformin were more likely to ovulate than those treated with Myo-inositol (p-0.001). The pregnancy rate per ovulatory cycle was lower (21.1%) in Group-B than in Group-A (29.9%) but equivalent to those in the literature, 22% and 24% in the study by Lopez *et al*.[14] separately. pregnancy was higher (21.1%) in our Group A. Another analogous study reported that pregnancy was approximately twice as likely when clomiphene induced ovulation with metformin as when stimulated by metformin only.[15] Our study did not report a mechanism for improved fertility per ovulation with clomiphene and metformin.

In one study, ovulation-resistant patients, when given myo-inositol (4000mg) in combination with clomiphene citrate, (72.2%) ovulated and (42.6%) became pregnant. The index study combined clomiphene and myoinositol (2000mg); ovulation occurred only in 32.6% and pregnancy in 29%.[16] Similarly, a pregnancy rate of (15.1%) is testified in myo-inositol and folic acid users in one study.[17]

Quite a few studies compared metformin with clomiphene citrate in polycystic infertile women. In one study, 626 women were administered six cycles of three randomised medical treatments, including metformin 1gm twice daily combined with placebo, clomiphene citrate combined with placebo, or metformin with clomiphene citrate.[18] Live birth rates with the metformin alone group were considerably lower than the two other groups with the combination. gadalla *et al*. in 228 PCOS women, administered clomiphene citrate with metformin or clomiphene citrate with a placebo.

There were no substantial differences in ovulation rates (64% versus 72%), pregnancy rates (40% versus 46%) or live birth rates (19% versus 27%).[19] Both studies suggest that metformin and clomiphene citrate did not improve the reproductive outcomes when given in combination. On the contrary, combined use of metformin with clomiphene citrate in a small group analysis of women having BMI over 35 kg/m2 and insulin resistance did suggest a potential benefit. In other studies, the use of clomiphene citrate with metformin did suggest a potential benefit in a small group of women having BMI over 35kg/m2 and insulin resistance.[14,20]

LIMITATION OF STUDY

The conduction of the study at a single centre limits generalizability in our study. Further studies with an increased dose of Myoinositol of 4000mg may be conducted to expect an improved outcome.

CONCLUSION

Our study suggests using Clomiphene citrate with Metformin as a first-line therapy for sub-fertile women with polycystic ovary syndrome. It improves ovulation and causes fewer side effects than Clomiphene citrate with myo-inositol.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

SP & NI: Data analysis, drafting the manuscript, conception, approval of the final version to be published.

BZS & UY: Data acquisition, critical review, approval of the final version to be published.

NKN: Critical review, study design, data interpretation, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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