International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Rani C et al. Int J Reprod Contracept Obstet Gynecol. 2022 Nov;11(11):3005-3011
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20222785

Original Research Article

Effects of metformin plus myo-inositol compared to metformin alone as pre-treatment of ovulation induction in polycystic ovary syndrome with insulin resistance

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Received: 11 September 2022
Accepted: 01 October 2022

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting reproductive-age women. Insulin resistance (IR) is a common disorder, which may impair female fertility by causing ovulatory dysfunction. Lifestyle modification and insulin sensitizers are commonly used in the management of IR. This study aimed to compare the effects of metformin plus myo-inositol versus metformin alone as pre-treatment in ovulation induction in polycystic ovary syndrome with insulin resistance.
Methods: This prospective quasi-experimental study was conducted in the department of reproductive endocrinology and infertility, Bangabandhu Sheikh Mujib Medical University, Dhaka, from July 2020 to June 2021. A total of 52 insulin-resistant infertile PCOS women were included in this study, who were allocated into two groups by using odd-even numbers and given two different treatments.
Results: Mature follicles and mid-luteal serum progesterone levels were significantly higher in metformin plus myo-inositol group (60.9% versus 28.0% and (73.9% versus 44.0%) respectively. The ovulation rate was significantly higher in metformin plus myo-inositol group (73.9% versus 44.0%), and the pregnancy rate was higher in metformin plus myo-inositol group (26.92% versus 11.54%), but the difference was not statistically significant.
Conclusions: Ovulation rate was significantly higher in metformin plus myo-inositol group than metformin alone group. The pregnancy rate was higher in metformin plus myo-inositol group but no significant difference was found between the two groups.

Keywords: Insulin resistance, Metformin, Myo-inositol, Ovulation induction, PCOS

INTRODUCTION

Polycystic ovary syndrome (PCOS) is considered the commonest cause of anovulatory infertility and prevalence of about 5 to 10% among women of the reproductive age group.[1] Anovulation constitutes about 40% of all female subfertility.[2] Women with PCOS have been classified into WHO group II anovulatory infertility. About 50% of PCOS patients suffer from infertility due to ovulation dysfunction.[3] According to the Rotterdam ESHRE/ ASRM-sponsored PCOS consensus workshop group 2004, PCOS is diagnosed by at least two out of three features: presence of oligo and/or anovulation, evidence of clinical and/or biochemical hyperandrogenism, and ultrasound appearance of polycystic ovaries.[4] Almost 50 to 75% of PCOS women are insulin resistant.[5] Hyperinsulinemia due to insulin resistance occurs in approximately 80% of PCOS women with central obesity and 30 to 40% of lean women with the polycystic ovarian syndrome.[6,7] The last few decades of research have recognized the central role of insulin resistance with compensatory hyperinsulinemia and hyperandrogenism in the pathogenesis of endocrine. The main treatment modalities for infertile PCOS women are dietary and

lifestyle modifications, insulin sensitizers, oral ovulation induction agents, gonadotropins, and laparoscopic ovarian drilling. Insulin sensitizers are recommended to improve endocrine and metabolic abnormalities of insulin-resistant PCOS which facilitate ovarian folliculogenesis and improve ovulation and minimize the long-term health hazard of PCOS.[8] Insulin sensitizers improve hyperandrogenemia and ovulatory functions.[9] Among insulin sensitizers, Metformin is commonly used in clinical practice. Metformin reduces intestinal glucose absorption, and hepatic gluconeogenesis and increases glucose uptake by some peripheral tissues. However, it is the first insulin-sensitizing drug to be used in PCOS women to investigate the role of insulin resistance in the pathogenesis of the syndrome and there is evidence that it may have metabolic, endocrine, and reproductive benefits.[10] Recent studies have reported relevant evidence on Myo-inositol as a newer insulin-sensitizing agent for PCOS. It acts as a post-receptor mediator or second messenger of insulin signalling and leads to improvement in ovulation and restoring fertility. Myo-inositol supports glucose entry into the cell. A study on PCOS shows a decrease in hyperandrogenemia and improvement in ovulation and restoring fertility after treatment of Myo-inositol.[11] It enhances oocyte and follicle maturation, and also improves oocyte and embryo quality. While metformin is the classical and most frequently used molecule for the treatment of PCOS, the focus on myo-inositol is comparatively recent.[12] The inference may be made that two drugs acting synergistically have more hormonal, clinical, and reproductive benefits as compared to when one drug is given alone. It has been hypothesized that the use of combined metformin and myo-inositol as pre-treatment may improve ovulation in insulin-resistant PCOS compared to metformin alone. Anovulatory PCOS with hyperinsulinemia are typically more resistant to ovulation-inducing agents. Most of these patients need gonadotropin or LOD for ovulation induction. This imposes a financial burden and physical risk on PCOS women. To reduce these risks, some new studies suggest the combined use of metformin and myo-inositol as pre-treatment, which may improve the efficacy of oral ovulation induction.

So, with this background, the study was conducted to explore the beneficial effects of metformin plus myo-inositol versus metformin alone as pre-treatment in ovulation induction in polycystic ovary syndrome with insulin resistance.

METHODS

This prospective quasi-experimental study was conducted in the department of reproductive endocrinology and infertility, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka between July 2020 to June 2021.

The study was started after approval by the Institutional Review Board of BSMMU.

Inclusion criteria

Inclusion criteria were age 18 to 40 years, diagnosed cases of PCOS patients according to Rotterdam criteria, primary or secondary infertility, presence of acanthosis nigricans, and HOMA-IR>1.8.

Exclusion criteria

Women having BMI≥30 kg/m^2, diabetes mellitus (fasting glucose ≥7 mmol/l), uncontrolled hypothyroidism, bilateral tubal block, renal or liver disease, abnormal semen parameter of husband, and FSH>10 IU/l were excluded from the study.

Patients were instructed not to take oral contraceptives, anti-androgens, or any drug for at least three months before starting study that could influence hormonal metabolism and ovulation. After maintaining inclusion and exclusion criteria, total 52 insulin resistant infertile PCOS women with 18 to 40 years were included in this study. After full explanation of the study procedure, informed written consent was taken from the couple. Baseline investigations Including hormonal parameters were done. Insulin sensitivity was measured with homeostatic model assessment of insulin resistance (HOMA-IR). HOMA-IR >1.8 was accepted as insulin resistance. Total study populations were divided into two groups: twenty-six patients (group A) assigned by odd numbers, who were receiving metformin with myo-inositol, and twenty-six patients (group B) assigned by even numbers, who were receiving metformin alone. Group A was treated as pre-treatment with metformin (Tablet Comet-Square Pharma) 500 mg three times daily and myo-inositol (Tablet Ovacare myo-A Meyer Vitabiotics) 1000 mg two times daily for 12 weeks. Group B was treated as pre-treatment with only Metformin for same dose and duration. After 12 weeks, myo-inositol was stopped, but metformin was continued during rest of study period in both groups. During 12 weeks of pre-treatment, 3 patients conceived spontaneously in group A and 1 patient conceived in group B, were excluded from subsequent analysis. After 12 weeks, both groups (23 patients in group A) and (25 patients in group B) received tablet letrozole (Letrol-Square Pharma) 5 mg starting from day 2/3 of menstrual cycle (spontaneous or induced withdrawal bleeding) for 5 days. All participants were instructed not to take any medications during the study period except after consulting with the doctor.

Transvaginal sonography (TVS) was done on day 12 to evaluate size and number of developing ovarian follicles and endometrial thickness. If leading follicle size was ≥18 mm in diameter, 5000 iu HCG was given intramuscularly. Patients were advised for timed sexual intercourse and pregnancy test in case of missed periods. Mid-luteal serum progesterone was measured. Serum progesterone level >3 ng/ml was presumptive of ovulation. The primary outcome of this study was ovulation rate which was determined by the presence of mature follicles on day 12 and/or mid-

luteal serum progesterone. Ovulation was diagnosed when at least one leading follicle reaching ≥18 mm in diameter was observed by TVS on day 12 and/or mid-luteal serum progesterone level >3 ng/ml at the follow-up visit. The secondary outcome was the pregnancy rate.

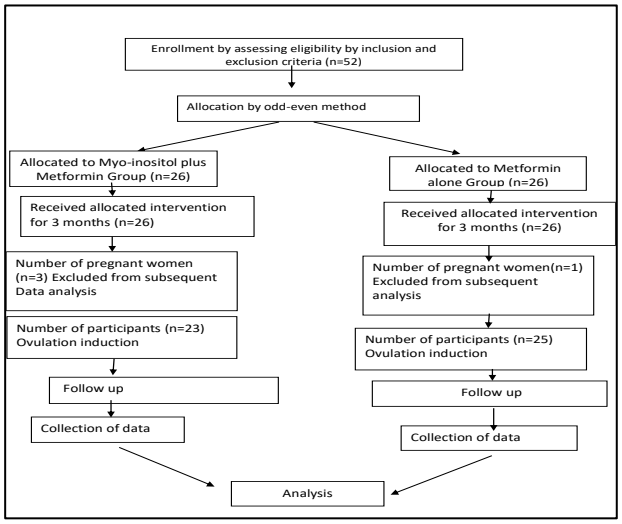

Figure 1: Flow chart for the methodology.

For each and every subject separate data collection sheet was prepared. Data were collected form the patients on different visits on variables of interest using interview, observation, clinical examination, investigations and from the history sheet of the patients. The cumulative data were subjected to analysis. Statistical analyses were carried out by the SPSS program for Windows, version 22.0 (SPSS, Chicago, IL). The mean±SD values were calculated for continuous variables and percentages for categorical values. Data was tested using the unpaired t-test and chi-square test as appropriate. P value <0.05 was considered statistically significant. Ethical clearance was taken from the Institutional Review Board of BSMMU to perform the investigation and study. The aims and objectives of the study along with its procedure, alternative diagnostic methods, risks, and benefits were explained to the patient in detail, in an easily understandable local language, and then voluntary informed written consent was taken from the couple before collecting data. Privacy, anonymity, and confidentiality were maintained during the procedure.

RESULTS

In this study, a total of 52 diagnosed cases of insulin-resistant PCOS women with infertility were included. Among them, 26 patients received metformin plus myo-inositol (group A) and 26 patients received metformin alone (group B). After 12 weeks of pre-treatment, Letrozole was given in both groups for ovulation induction. 3 participants dropped out in group A (metformin plus myo-inositol) and 1 in group B (metformin alone group). Because they were pregnant within 3 months of pre-treatment they were excluded from data analysis. So, after ovulation induction data analysis was done for 23 patients in group A and 25 patients in group B. Age, type of infertility, oligomenorrhea, hirsutism, polycystic ovary, waist circumference, and BMI were similar in both groups (Table 1).

Table 1: Baseline demographic, Rotterdam criteria, and clinical characteristics of study participants (n=52).

Demographic characteristics	Group A (metformin plus myo-inositol) (n=26)		Group B (metformin alone) (n=26)		P value
	N	%	N	%	
Age (years)					
≤20	5	19.2	10	38.5	
21-25	14	53.8	12	46.2	
26-30	7	26.9	4	15.4	
Mean±SD	24.4±3.7		22.8±3.8		0.125
Infertility					
Primary	18	69.2	20	76.9	0.532
Secondary	8	30.8	6	23.1	
Oligomenorrhea	24	92.3	23	88.5	0.500
Hirsutism	22	84.6	23	88.5	0.500
Polycystic ovary	18	69.2	20	76.9	0.532
Waist circumference (cm)	88.3±3.6		86.7±6.3		0.261
BMI (kg/m^2)	25.7±1.6		24.6±2.6		0.071

Data were expressed as frequency, percentage and mean±SD
Unpaired t-test for quantitative variables and Chi-square test for qualitative variables were done to analyse the data

The mean serum LH, FSH, TSH, fasting glucose, fasting insulin, HOMA-IR, and serum prolactin levels were almost similar between the two groups, which was not statistically significant when compared to the two groups (p>0.05) (Table 2). Mature follicles were present significantly higher in myo-inositol plus metformin group

than metformin alone group (60.9% versus 28.0%; p=0.021). Mean serum progesterone was statistically higher in metformin plus myo-inositol group than metformin alone group (12.67±9.98 ng/ml versus 7.26±7.68 ng/ml; p=0.040). The mean endometrial thickness was higher in Metformin plus myo-inositol group than metformin alone group (7.21±1.68mm versus 6.69±1.54 mm), but the difference was not statistically significant (p>0.05) between the two groups (Table 3).

Table 2: Hormonal and biochemical parameters (baseline) of study participants (n=52).

Parameters	Group A (n=26)	Group B (n=26)	P value
	Mean±SD	Mean±SD	
Serum LH (µIU/ml)	6.4±2.2	6.3±3.2	0.937
Serum FSH (µIU/ml)	5.2±1.4	5.3±1.7	0.867
TSH (µIU/ml)	2.0±1.2	2.5±1.4	0.184
Fasting glucose (mmol/l)	5.0±0.7	4.9±0.5	0.522
Fasting insulin (µIU/ml)	12.7±3.9	14.0±6.3	0.389
HOMA-IR	3.1±1.5	2.8±1.1	0.529
Serum prolactin (ng/dl)	16.2±6.6	15.0±6.8	0.506

Data were expressed as mean±SD
Unpaired t-test was done to analyse the data

Table 3: Comparison of outcome of ovulation induction (n=48).

	Group A (n=23)		Group B (n=25)		P value
	n	%	n	%	
Presence of mature follicles (≥18mm)					
Yes	14	60.9	7	28.0	*0.021
No	9	39.1	18	72.0	
Mid-luteal progesterone (ng/ml)					
≤3.0	6	26.1	14	56.0	
>3.0	17	73.9	11	44.0	
Mean±SD	12.67±9.98		7.26±7.68		*0.040
Endometrial thickness (mm)					
<7	9	39.1	14	56.0	
≥7	14	60.9	11	44.0	
Mean±SD	7.21±1.68		6.69±1.54		0.268

Data were expressed as frequency, percentage and mean±SD
Unpaired t-test for quantitative variables and Chi-square test for qualitative variables were done to analyse the data

The ovulation rate was significantly higher in metformin plus myo-inositol group than metformin alone group (73.9% versus 44.0%; p=0.035) which was statistically significant. The pregnancy rate was 7 (26.92%) in metformin plus myo-inositol group and 3 (11.54%) in metformin alone group, but the difference was not statistically significant (p>0.05) between the two groups (Table 4).

Table 4: Comparison of ovulation rate and pregnancy rate (n=52).

	Group A (n=26)		Group B (n=26)		RR (95% CI)	P value
	n	%	n	%		
Ovulation rate						
Yes	17	73.9	11	44.0	1.68 (1.01-2.78)	0.035
No	6	26.1	14	56.0		
Pregnancy rate						
Pregnant	7	26.92	3	11.54	2.33 (0.67-8.05)	0.159
Non pregnant	19	73.08	23	88.46		

P values were obtained by Chi-square (x2) test;
*P value <0.05 means the difference is statistically significant

DISCUSSION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder affecting reproductive-age women. Anovulation and infertility are the commonest effects of PCOS. Insulin resistance and compensatory hyperinsulinemia play pivotal roles in this syndrome. Several trials showed that insulin-sensitizing agents, such as Metformin and Myoinositol are the first-line pharmacological treatment to restore ovulation in women with PCOS. Both can be used individually or in combination to get an additive effect. There are several studies that explain the combined use of Metformin and Myoinositol and their better effects on endocrine, metabolic and reproductive outcome which is corresponding to our ideas in this research.[13-15] This study aimed to compare the effects of metformin plus myo-inositol versus metformin alone in insulin-resistant infertile polycystic ovary syndrome. The present study showed mean age was 24.4±3.7 years in metformin plus myo-inositol group and 22.8±3.8 years in metformin alone group, which was not statistically significant (p=0.125) (Table 1). Our data support what was recently reported by Begum et al, Thakur et al and Prabhakar et al.[13,16,17] We found primary infertility was more common in both groups, that was 18 (69.2%) in metformin plus myo-inositol group and 20 (76.9%) in metformin alone group, that was not statistically significant (p=0.532) (Table 1). An almost similar study conducted by Thakur et al and Prabhakar et al where found primary infertility was 75.0% in group A (metformin alone), 70.0% in group C (metformin plus myo-inositol), and 40 (70.20%) in group I (metformin plus myoinositol), 43 (72.90%) in group II (myoinositol) respectively.[18,17] This study observed mean serum LH, FSH, TSH, fasting glucose, fasting insulin, HOMA-IR, and serum prolactin levels were almost similar between the two groups, which was not statistically significant when compared between the two groups (p>0.05) (Table 2). Supporting my results, another study by Ozay et al showed that mean LH, FSH, TSH, fasting glucose, fasting insulin, HOMA-IR, and prolactin were

statistically not significant (p>0.05) between the two groups.[18] We found, large follicles (size ≥18.0 mm) were significantly higher in myo-inositol and metformin group (60.9% versus 28.0%) but small follicles (<14 mm) and intermediate follicles (14-17.9 mm) were higher in metformin alone group (13% versus 40%); (26.1% versus 32%), respectively. Artini et al reported, that their study group (myo-inositol group) presented a higher number of large-size follicles (diameter >16 mm) and a lower number of intermediate (>12-<16 mm) and small-size follicles (<12 mm) that was almost similar to this study.[19] Ozay et al described, that after 12 weeks of myo-inositol administration there was a significant increase in mid-luteal serum progesterone levels (p<0.01).[18] Similar results were observed in this study. Mid-luteal serum progesterone level >3.0 ng/ml was significantly higher in myo-inositol and metformin group (73.9% versus 44.0%) (Table 3). Ozay et al also reported that mean endometrial thickness at trigger day was higher (10.3±1.2 mm) in the myo-inositol group and the difference was not significant (p=0.13) which supports the present study.[18] We found endometrial thickness ≥7 mm was higher in myo-inositol and metformin group (60.9%). Mean endometrial thickness on day 12 was higher in myo-inositol and metformin group than metformin alone group (7.21±1.68 versus 6.69±1.54) but the difference was not statistically significant p>0.05) (Table 3). Mean endometrial thickness was higher in the previous study may be due to their study showing endometrial thickness at trigger day but this study reported day 12 endometrial thickness. We observed ovulation rate was significantly higher in myo-inositol and metformin group (73.9% versus 44.0%) (Table 4). A study done by Begum et al showed ovulation rate was significantly higher in metformin and myo-inositol group than metformin only the group, (77.50% versus 43.00%) which was almost similar to a recent study.[13] Agrawal et al reported ovulation rates were higher in myo-inositol and metformin group (34.8%vs 13.5%) in their first cycle of ovulation induction.[14] Their ovulation rate was low compared to the present study may be due to the use low dose of 50 mg tablet of clomiphene citrate. But, in this study tablet letrozole 5 mg was used for ovulation induction. Ozay et al reported, that after 3 months of myo-inositol being taken 73.4% of participants became ovulatory which supports the present study.[18] Kamenov et al showed after myo-inositol treatment spontaneous ovulation occurred in 61.7% of women and after adding Tab clomiphene 72.2% of women ovulated.[20] That study was comparable to a recent study. Raffone et al reported, that after 6 months of myo-inositol administration sixty-five percent (65%) of participants restored spontaneous ovulation activity documented by follicular growth at ultrasound evaluations and increased serum progesterone concentrations in the luteal phase.[21] That findings were comparable to the current study. Papaleo et al reported, that after Myo-inositol administration, 72% presented monthly spontaneous ovulation activity.[12] Ovulation was documented by follicular growth and increased serum progesterone concentrations in the luteal phase. The findings of that study were also comparable to the present study. In the present study, the total pregnancy rate was higher in myo-inositol and metformin group (26.92% versus 11.54%) but the difference was not statistically significant when compared between the two groups (Table 4). A similar study done by Agrawal et al consisted, at first cycle conception rate was higher in myo-inositol and metformin group than in metformin only group (19.6% versus 7.7%), which was not significant that is almost similar to the present study (17.3% versus 8%).[14] Begum et al reported, that the total pregnancy rate was significantly higher in the metformin and myo-inositol group than metformin only the group (43.75% versus 25%), which was higher than my study may be due to more induction cycles and a large sample size.[13] Myo-inositol is generally well tolerated in therapeutic doses, with minor side effects reported at higher concentrations. We added 2 gm myo-inositol daily along with metformin to reduce the dose and price of myo-inositol instead of recommended 4 gm by other authors. We compared the effect of this low dose of myo-inositol along with metformin versus only metformin in insulin-resistant infertile PCOS women. To get a satisfactory result, reducing the cost of myo-inositol would be very helpful for our patients. Our main outcome measure was the ovulation rate. So, we did not look for biochemical tests after 3 months of pre-treatment. Because it is well established by many studies, endocrine and metabolic profile improved after treatment with metformin or myo-inositol.

The study was conducted during the COVID pandemic situation and locked down period. Serial transvaginal sonography was appropriate for the determination of ovulation that was not done in the current study to minimize the exposure risk of COVID-19 infection. Rupture of follicle could not be detected for confirmation of ovulation due to the locked down period. One cycle of ovulation induction was given due to data collection with follow-up was challenging for the COVID-19 situation. Further studies with larger sample sizes, longer duration follow-up, and multiple induction cycles are warranted to support these findings.

CONCLUSION

The ovulation rate was significantly higher in metformin plus myo-inositol group than in the metformin alone group. Though there was an increased pregnancy rate in metformin plus myo-inositol group but no statistically significant difference was found between the two groups.

ACKNOWLEDGMENTS

The authors would like to thank the supervisor of this thesis work and other teaching faculty members of the department of reproductive endocrinology and infertility, the infertile PCOS women who have been part of the study, and those who supported the investigation facilities in the allied Departments of Bangabandhu Sheikh Mujib Medical University.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Rani C, Deeba F, Ishrat S, Banu J, Jahan S, Nazneen S, et al. Effects of metformin plus myo-inositol compared to metformin alone as pre-treatment of ovulation induction in polycystic ovary syndrome with insulin resistance. Int J Reprod Contracept Obstet Gynecol 2022;11:3005-11.