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Efficacy And Safety of Myo Inositol in The Treatment of Polycystic Ovary Syndrome Patients Comparison with Metformin

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Background: In polycystic ovary syndrome (PCOS), changes in physical appearance, e., weight gain, hirsutism, menstrual disturbances and infertility result in reduced quality of life. Metformin and Myo-inositol, being insulin sensitisers, improve biochemical, clinical and reproductive parameters in PCOS women. This study was done to compare the efficacy and safety of Myo-inositol versus Metformin among PCOS women.

Methodology: This open-label randomised control trial was conducted over 1 year in the Department of Gynaecology & Obstetrics, Rajshahi Medical College Hospital, Rajshahi. A total of 100 women with polycystic ovarian syndrome were enrolled and randomly (by simple lottery method) divided into two treatment groups: group A (Tab. Myo-inositol 1g twice daily for 6 months) and group B (Tab. Metformin 500 mg thrice daily for 6 months). After taking informed consent, by face-to-face interview, baseline data will be collected consecutively from polycystic ovarian syndrome with the help of a semi-structured questionnaire. Both groups were followed up at the end of the third and sixth months of the whole drug therapy period. The data were analysed via SPSS (version 24.0).

Results: The Mean age of all study subjects was 24.24±3.47 SD (years). Mean Ferriman-Gallwey score and Luteinizing hormone were higher among group B than group A at the end of 6 months ($p<0.05$). After 6 months of treatment, regular menstrual cycles increased by 38% and 26% ($p>0.05$) while acne reduced by 26% and 14% in group A and B, respectively ($p=0.021$). Vomiting, generalised weakness, and flatulence were significantly higher in the metformin group than the myo-inositol group after 6 months ($p<0.05$).

Conclusion: In the treatment of PCOS patients, myo-inositol is as effective as metformin and has a better safety profile. However, further larger multicenter studies are warranted.

Keywords: Myo Inositol, Polycystic Ovary Syndrome, Metformin

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Introduction

Polycystic ovary syndrome (PCOS), also known as Stein-Leventhal syndrome, is one of the most common endocrine abnormalities among premenopausal women, yet its diagnosis remains one of the most challenging issues in endocrinology and reproductive medicine. It has been recognised as the most frequent endocrinopathy among reproductive-aged women [1]. The prevalence is generally considered to be between 6-20%, depending on the definition and the population studied. This syndrome is heterogeneous by nature and is characterised by a combination of signs and symptoms of androgen excess and ovarian dysfunction in the absence of other specific diagnoses. Women with PCOS often present in their adolescence or early adulthood with symptoms of oligomenorrhoea or hirsutism, or infertility. Up to 70% of affected women remain undiagnosed or have long delays before the condition is recognised [2]. There is a recent rise in PCOS cases in urban India because of westernisation, modernisation, stress and lifestyle changes. It is a complex, heterogenous, multisystem condition characterised by elevated androgen levels, menstrual irregularities, and/or small cysts on one or both ovaries. It can present with a wide spectrum of clinical features and delayed sequelae like type 2 diabetes mellitus, cardiovascular diseases, metabolic syndrome and endometrial cancer, which are preventable. It is caused by an imbalance of sex hormones that leads to menstrual irregularities, infertility, anovulation and other metabolic disturbances [3]. Although it was previously considered a disorder of adult women, recent evidence suggests that PCOS is a lifelong syndrome, manifesting since prenatal age. It is a significant public health issue. The most common abnormalities associated with PCOS include menstrual disorders (amenorrhoea or oligomenorrhoea), often leading to infertility (in 73-75% of the cases), abdominal obesity (30-70%) and type 2 diabetes (approximately 10%). The health risks associated with PCOS, however, go far beyond management of these features and likely extend past the reproductive years through and beyond menopause. Women present with diverse features including psychological (anxiety, depression, body image and impaired quality of life), reproductive (irregular menstrual cycles, hirsutism, Infertility and pregnancy complications) and significant metabolic features (insulin resistance, metabolic syndrome, prediabetes, type 2 diabetes mellitus and cardiovascular risk factors). Metformin and Myo-inositol, being insulin sensitisers, improve hyperandrogenic and reproductive features in PCOS in women [4]. Several trials showed that insulin sensitiser agents, such as metformin and MI, are the first-line treatment to restore normal menstrual cycles in women suffering from PCOS, suggesting that an endocellular defect of the precursor of IPG, such as MI and/or DCI might trigger the compensatory hyperinsulinemia in most PCOS subjects [5]. In PCOS, ovarian dysfunction usually manifests as oligomenorrhoea/ amenorrhoea resulting from chronic oligo-ovulation/anovulation. The majority of PCOS patients have ovarian dysfunction, with 70% to 80% of women with PCOS presenting with oligomenorrhoea or amenorrhoea. The clinical and/or biochemical signs of androgen excess in PCOS result from increased synthesis and release of ovarian androgens. PCOS is a common cause of hirsutism occurring in approximately 60% of cases; however, this varies with race and degree of obesity [6]. Hirsutism should be assessed with a standardised scoring system, i.e. modified Ferriman-Gallwey (mFG) score, which is also used in India [7]. The present study was conducted for need for demonstrate the efficacy and safety of Myo-inositol because of its limited studies available in Bangladesh till now regarding the supplementation of Inositol in PCOS treatment. The study aimed to determine the effectiveness of Myo-Inositol over Metformin in women with an established diagnosis of PCOS.

Material and Methodology

Study design: It was an open-label randomised controlled trial.

Study place: Department of Obstetrics & Gynecology, Rajshahi Medical College, Rajshahi, Bangladesh.

Study period: This study was carried out over 1 year from April 2021 to March 2022.

Study population: In this study, the study population were women with polycystic ovarian syndrome from the OPD of the Gynecology & Obstetrics department, Rajshahi Medical College Hospital, Rajshahi.

The patients were randomly divided into two groups of 50 each to receive either of the following two treatments. Group A (Experimental group): Women with polycystic ovarian syndrome who were treated by Tab Myo-inositol 1g twice daily for 6 months were recruited as group A.Group B (Control group): Women with polycystic ovarian syndrome who were treated by Tab. Metformin 500 mg thrice daily for 6 months was recruited as group B.

Sampling method: Patients with PCOS were enrolled consecutively in this study.

Sample size: The sample size was determined by hypothesis testing of the difference between two proportions [9] as follows:

$$n = \frac{p_1(100-p_1)+ p_2(100-p_2)}{(p_1-p_2)^2} \times (Z_\alpha + Z_\beta)^2$$

$p_1 = proportion\ of\ regular\ cycle\ who\ had\ taken\ Myo-inositol$

The sample size was determined by the following formula:

P2 proportion of regular cycle who had taken Metformin

Z α= 1.96 at 5% level, z value of SND at a given level of significance

Due to time and funding constrain as well as a lack of availability of patients in the COVID-19 pandemic, finally 50 respondents in each group were taken.

Selection Criteria:

Inclusion criteria:

The cases were reproductive age women who met the diagnostic criteria for PCOS. Diagnosis of PCOS was established based on the Rotterdam 2003 consensus, which was the finding of 2 out of the 3 following criteria:

1. Oligo and/or anovulation;
2. Hyperandrogenism, defined as hirsutism (Ferriman-Gallwey score>8), or minor signs such as acne, seborrhea, and
3. Criteria for polycystic ovary by ultrasound examination (minimum of 12 follicles with 2–9 mm diameters in each ovary and/or increasing ovarian volume with a minimum size of 10 mm3)

The patients were randomly divided into two groups. Each 50 patients received either of the following two drugs:

Group A (Experimental group): Women with polycystic ovarian syndrome who were treated by Tab Myo-inositol 1g twice daily for 6 months were recruited as group A. Group B (Control group): Women with polycystic ovarian syndrome who were treated by Tab. Metformin 500 mg thrice daily for 6 months were recruited as group B.

Exclusion criteria:

The Exclusion criteria were women suffering from

1. Any history of drug intake- Anti diabetic (or) oestrogen and progesterone
2. Women with a previous history of hyperprolactinemia, Cushing's disease, Hypothyroidism/Hyperthyroidism, Active liver disease, renal impairment, or established type 1 or type 2 diabetes mellitus.
3. Any neoplastic disease
4. Respondents who did not give consent to participate and were unable to come for regular follow-ups.

Data collection technique

After describing the aim, purpose and procedure of the study, a total of 100 cases were selected based on inclusion and exclusion criteria. Informed written consent was taken from each participant or their caregiver. The patients were randomly divided into two groups by a simple lottery method for drug allocation, of whom 50 each received either of the following two treatments. Women with polycystic ovarian syndrome who were treated by Tab Myo-inositol 1g twice daily for 6 months were recruited as group A, and women with polycystic ovarian syndrome who were treated by Tab.

Metformin 500 mg thrice daily for 6 months was recruited as group B. All the women of both group A & B were subjected to take detailed history, including socio-demographic, parity, clinical/medical history and height, weight were measured. Clinical history included complaint of oligomenorrhea, hirsutism, and examination included the FG score and BMI. Oligomenorrhea was defined as fewer than eight menstrual cycles during the previous 12 months or a menstrual interval of more than 35 days. Clinical hyperandrogenism was defined as a Ferriman-Gallwey score of >8. PCOS was diagnosed when either ovary on ultrasound had more than 12 follicles with a diameter of 2 - 9 mm or when ovarian volume was more than 10 cm^3.

A detailed general examination was conducted for identification of acne, hirsutism and acanthosis nigricans. Standard operating procedure for anthropometric measurements done like: Weight: The subjects stand, lie or sit in centre of balance scale platform with minimal clothing and no shoes worn, weighing machine having 100gm accuracy. Height/Length: It was measured using a measuring tape. The tape was fixed to wall vertically, and height was measured by making subject stand with heels in apposition with wall, taking care that there was no bending of knees. Measurement was taken to nearest 0.5 cm. All investigations were performed in same laboratory, according to standard procedures. Hormonal assays for serum FSH, LH, and estradiol were performed using chemiluminescent immunoassay. Trans abdominal ultrasound/TVS was performed for all women to detect PCOS. Results of above laboratory investigations and imaging studies were recorded along with clinical data of patient in a proforma data sheet. Results of above laboratory investigations and imaging studies will be recorded along with clinical data of patient in a data sheet. Assessment of efficacy of drugs was done by observing improvement of signs and symptoms. i.e. regularity of menstrual cycle, hirsutism (using modified Ferriman Gallwey score- a score of 0 (none) to 4 (severe) in nine areas of body is assigned with maximum possible score of 36. Scores < 4 indicate mild hirsutism, 4-7 indicate moderate hirsutism ≥ 8 indicate severe hirsutism. Polycystic ovarian morphology, hormonal & anthropometric parameters like weight changes at end of 3 (12 weeks) & 6 (24 weeks) months throughout respective drug therapy. Safety of drugs was assessed by any other adverse effects reported by patient or patient's guardian were recorded in both groups.

Safety assessment was done at the end of 12 and 24 weeks following the drug administration. The patients were observed for the incidence of various adverse drug reactions (ADRs) or the side effects like nausea, vomiting, diarrhea, abdominal cramps, flatulence, generalised weakness, headache, dizziness, menorrhagia, megaloblastic anemia and lactic acidosis.

Data Collection Tools

On obtaining ethical clearance from the Ethical Committee of Rajshahi Medical College, Rajshahi and the patient of PCOS who gave voluntary consent to participate in this study were included as a sample, and the data collection was commenced with the help of semi semi-structured questionnaire, measuring tape and weight machine. Appropriate investigation of this study was done in a standard, good-quality laboratory with respective appropriate equipment.

Data processing and analysis

After collecting data, the questionnaires were categorised into groups. Then I checked the completeness and internal consistency of questions. The data were analysed via Statistical Package for the Social Sciences (SPSS, version 24.0) software. Qualitative variables were described by frequency distribution, while quantitative variables were described by the mean and standard deviation. Mean ± Standard Deviation (SD) of all the parameters of interest were calculated for both groups of patients separately, and the difference of means between the two groups was tested by unpaired 't' test. The chi-square test was applied for categorical data. The statistical significance was evaluated as an appropriate probability level, $p < 0.05$ for all tests.

Results

Table 1: Sociodemographic characteristics of two study groups (n=100).

Sociodemographic variables		Total N (%)	Group A N (%)	Group B N (%)	p-value
Age group (Years)	≤20 years	11 (11.0)	5 (10.0)	6 (12.0)	0.856*
	21-25 years	59 (59.0)	29 (58.0)	30 (60.0)	
	26-30 years	27 (27.0)	15 (30.0)	12 (24.0)	
	31-35 years	3 (3.0)	1 (2.0)	2 (4.0)	
Age (Mean±SD), years		24.22±3.27	24.20±3.09	24.24±3.47	0.952†
Marital Status	Married	83 (83.0)	39 (78.0)	44 (88.0)	0.183*
	Unmarried	17 (17.0)	11 (22.0)	6 (12.0)	
Occupation	Unemployed	1 (1.0)	1 (2.0)	0	0.246*

	Daily worker	4 (4.0)	3 (6.0)	1 (2.0)	
	Service holder	17 (17.0)	10 (20.0)	7 (14.0)	
	Business	4 (4.0)	2 (4.0)	2 (4.0)	
	Homemaker	71 (71.0)	31 (62.0)	40 (80.0)	
	Others	3 (3.0)	3 (6.0)	0	
Residence	Urban	70 (70.0)	33 (66.0)	37 (74.0)	0.383*
	Rural	30 (30.0)	17 (34.0)	13 (26.0)	
Educational qualification	No formal education	11 (11.0)	7 (14.0)	4 (8.0)	0.599*
	Primary	24 (24.0)	10 (20.0)	14 (28.0)	
	Secondary	43 (43.0)	23 (46.0)	20 (40.0)	
	Graduate and above	22 (22.0)	10 (20.0)	12 (24.0)	
Monthly Family Income	≤20000 BDT	35 (35.0)	19 (38.0)	16 (32.0)	0.574*
	20001-40000 BDT	55 (55.0)	25 (50.0)	30 (60.0)	
	>40000 BDT	10 (10.0)	6 (12.0)	4 (8.0)	

Group A: Tab. Myo-inositol 1g twice daily Group B Tab. Metformin 500mg thrice daily, *P value determined by chi-square test, †P value determined by independent t-test. No significant difference was seen between groups regarding sociodemographic data(p>0.05).

Table 2: Comparison of changes in arthrometry in both groups (n=100).

	Weight			BMI		
	Group A (n=50)	Group B (n=50)	p-value*	Group A (n=50)	Group B (n=50)	p-value*
Baseline	62.38±2.65	61.77±4.49	0.415	26.58±3.14	27.57±4.91	0.232
After 3	60.79±2.29	60.33±4.16	0.491	25.89±2.89	26.91±4.70	0.194
months	†	†		†	†	
After 6	59.15±2.00	58.72±4.10	0.505	25.18±2.65	26.19±4.57	0.179
months	‡	‡		‡	‡	

The mean baseline, after 3 months and 6 months, weight and body mass index (BMI)in between groups were statistically insignificant (p>0.05). Baseline, after 3 months and 6 months, clinical and biochemical parameters among group A patients are given below.

Table 3: Baseline, after 3 months and after 6 months clinical and biochemical variables of group A (Myo-inositol) population (n=50).

Variables	Baseline	After 3 months	After 6 months
Weight, Kg	62.38±2.65	60.79±2.29	59.15±2.0
BMI, Kgm-2	26.58±3.14	25.89±2.89	25.18±2.65
Menstrual cycle			
Regular	10 (20.0%)	17 (34.0%)	29 (58.0%)
Irregular	40 (80.0%)	33 (66.0%)	21 (42.0%)
PCOM on USG	41 (82.0%)	23 (46%)	5 (10.0%)
FG score	11.18±5.01	8.7±5.04	5.52±4.25
Acne	16 (32.0%)	8 (16.0%)	4 (8.0%)
Acanthosis	4 (8.0%)	3 (6.0%)	1 (2.0%)
FSH (mIU/mL), Mean±SD	6.82±0.48	7.17±0.5	7.41±0.41
LH (IU/L), Mean±SD	12.69±1.44	11.75±1.46	11.28±1.26

BMI: Body mass index; **FG score:** Ferriman-Gallwey score; **FSH:** Follicle stimulating hormone; **LH:** Luteinizing hormone

Baseline, after 3 months and 6 months, clinical and biochemical parameters among group B patients are given below.

Table 4: Baseline, after 3 months and after 6 months clinical and biochemical variables of group B (Metformin) population (n=50).

Variables	Baseline	After 3 months	After 6 months
Weight, Kg	61.77±4.5	60.33±4.16	58.72±4.10
BMI, Kgm-2	27.57±4.91	26.91±4.70	26.19±4.57
Menstrual cycle			
Regular	12 (24.0%)	18 (36.0%)	25 (50.0%)
Irregular	38 (76.0%)	32 (64.0%)	25 (50.0%)
PCOM on USG	39 (78.0%)	29 (58.0%)	8 (16.0%)
FG score	11.62±6.73	10.28±6.18	9.0±5.38
Acne	18 (36.0%)	15 (30.0%)	11 (22.0%)
Acanthosis	5 (10.0%)	4 (8.0%)	3 (6.0%)
FSH (mIU/mL), Mean±SD	6.72±0.56	7.29±0.59	7.51±0.55
LH (IU/L), Mean±SD	12.80±1.60	12.09±1.55	11.86±1.40

BMI: Body mass index; **FG score:** Ferriman-Gallwey score; **FSH:** Follicle stimulating hormone; **LH:** Luteinizing hormone

Table 5: Comparison of changes in Ferriman-Gallwey Score (FG score) for assessment of hirsutism in both the groups (n=100).

Ferriman-Gallwey Score	Group A (n=50)	Group B (n=50)	p-value*
Baseline	11.18±5.01	11.62±6.73	0.712
After 3 months	8.70±5.04†	10.28±6.18†	0.164
After 6 months	5.52±4.25‡	9.0±5.38‡	0.001

Group A: Tab. Myo-inositol 1g twice daily Group B: Tab. Metformin 500mg thrice daily

*P value determined by an independent t-test

There was a reduction by 5.66 with Myo-inositol (group A) and a reduction by 2.62 with Metformin (group B) in reducing the FG score (Ferriman-Gallwey Score) (parameter for assessment of hirsutism) at the end of 6 months.

A fall in score at the end of 3 months was observed with myo-inositol as compared to metformin (2.48 vs 1.34, respectively). Mean FG score was significantly reduced among group A than group B at the end of 6 months (p=0.001).

Table 6: Comparison of changes in FSH and LH in both groups (n=100).

	FSH			LH		
	Group A (n=50)	Group B (n=50)	p-value*	Group A (n=50)	Group B (n=50)	p-value*
Baseline	6.82±0.48	6.72±0.56	0.316	12.69±1.44	12.80±1.60	0.702
After 3	7.17±0.50	7.29±0.59	0.308	11.75±1.46	12.09±1.55	0.264
months	†	†		†	†	
After 6	7.41±0.41	7.51±0.55	0.279	11.28±1.26	11.86±1.40	0.030
months	‡	‡		‡	‡	

Group A: Tab. Myo-inositol 1g twice daily Group B Tab. Metformin 500mg thrice daily

FSH: Follicle-stimulating hormone; **LH:** Luteinizing hormone

The mean value of FSH among group A and group B in baseline, at the end of 3 months and 6 months showed no significance. Mean LH was significantly higher among group B than group A at the end of 6 months (p=0.03).

Table 7: Comparison between groups regarding changes in menstrual cycle and skin problems (n=100).

		Group A(n=50)	Group B(n=50)	p-value*
Regular menstrual cycle	Baseline	10 (20.0%)	12 (24.0%)	0.629
	After 3 months	17 (34.0%)	18 (36.0%)	0.834
	After 6 months	29 (58.0%)	25 (50.0%)	0.422
Acne	Baseline	16 (32.0%)	18 (36.0%)	0.673
	After 3 months	8 (16.0%)	15 (30.0%)	0.096
	After 6 months	3 (6.0%)	11 (22.0%)	0.021
Acanthosis nigricans	Baseline	4 (8.0%)	5 (10.0%)	0.727
	After 3 months	3 (6.0%)	4 (8.0%)	0.695
	After 6 months	1 (2.0%)	3 (6.0%)	0.307

Group A: Tab. Myo-inositol 1g twice daily Group B Tab. Metformin 500mg thrice daily

*P value determined by chi-square test

Both drugs showed improved menstrual cycles. The percentage of women with regular menstrual cycles increased by 14% and 12% at the end of 3 months in the myo-inositol and metformin groups, respectively, while it increased by 38% and 26% at the end of 6 months in the groups, respectively. Acne before treatment was noted in 32% of women in group A and 36% in group B. After 6 months of treatment, Acne in group A is reduced by 26% and in group B by 14% which is significant (p=0.021).

Table 8: The incidence of various adverse drug reactions (ADRs) among group A patients (n=50).

Adverse Drug Reaction	3 months aftern (%)	6 months aftern (%)
Nausea	4 (8.0)	6 (12.0)
Vomiting	2 (4.0)	2 (4.0)
Diarrhea	2 (4.0)	4 (8.0)
Abdominal Cramp	2 (4.0)	2 (4.0)
Generalized weakness	1 (2.0)	1 (2.0)
Menorrhagia	12 (24.0)	11 (22.0)
Flatulence	0	0
Headache	0	0
Dizziness	5 (10.0)	4 (8.0)
Lactic acidosis	0	0

Adverse reactions of myo-inositol group patients in different follow-ups showed that menorrhagia (24% and 22%), dizziness (10.0% and 8.0%), and nausea (8% and 12%) were major adverse reactions at the end of 3 months and 6 months, respectively.

Table 9: The incidence of various adverse drug reactions (ADRs) among group B patients (n=50).

Adverse Drug Reaction	3 months aftern (%)	6 months aftern (%)
Nausea	15 (30.0)	12 (24.0)
Vomiting	8 (16.0)	10 (20.0)
Diarrhea	4 (8.0)	3 (6.0)
Abdominal Cramp	5 (10.0)	7 (14.0)
Generalized weakness	13 (26.0)	10 (20.0)
Menorrhagia	0	0
Flatulence	11 (22.0)	8 (16.0)
Headache	3 (6.0)	2 (4.0)
Dizziness	6 (12.0)	5 (10.0)
Lactic acidosis	1 (2.0)	1 (2.0)

Adverse reaction of metformin group patients in different follow ups showed that, nausea (30% and 24%), vomiting (16% and 20%), weakness (26% and 20%), abdominal cramp (10% and 14%), flatulence (22.0% and 16.0%) etc. were majoradverse reactions at the end of 3 months and 6 months respectively.

Table 10: Comparison of ADRs (Adverse drug reactions) between groups at 3 months (n=100).

Adverse drug reactions	At 3 months		p-value
	Group A	Group B	
Nausea	4 (8.0%)	15 (30.0%)	0.005
Vomiting	2 (4.0%)	8 (16.0%)	0.046
Diarrhea	2 (4.0%)	4 (8.0%)	0.40
Abdominal Cramp	2 (4.0%)	5 (10.0%)	0.240
Generalized weakness	1 (2.0%)	13 (26.0%)	0.001
Menorrhagia	12 (24.0%)	0	<0.001
Flatulence	0	11 (22.0%)	<0.001
Headache	0	3 (6.0%)	0.079
Dizziness	5 (10.0%)	6 (12.0%)	0.749
Lactic acidosis	0	1 (2.0%)	0.315

Group A: Tab. Myo-inositol 1g twice daily Group B Tab. Metformin 500mg thrice daily

After 3 months, the incidence of nausea, vomiting, generalised weakness, and flatulence was observed more with metformin (group B), and this difference was statistically significant (p<0.05).

Table 11: Comparison of ADRs (Adverse drug reactions) between groups at 6 months (n=100).

Adverse drug reactions	At 6 months		p-value
	Group A	Group B	
Nausea	6 (12.0%)	12 (24.0%)	0.118
Vomiting	2 (4.0%)	10 (20.0%)	0.014
Diarrhea	4 (8.0%)	3 (6.0%)	0.695
Abdominal Cramp	2 (4.0%)	7 (14.0%)	0.081
Generalized weakness	1 (2.0%)	10 (20.0%)	0.004
Menorrhagia	11 (22.0%)	0	<0.001
Flatulence	0	8 (16.0%)	0.003
Headache	0	2 (4.0%)	0.153
Dizziness	4 (8.0%)	5 (10.0%)	0.727
Lactic acidosis	0	1 (2.0%)	0.315

Group A Tab.. Myo-inositol 1g twice daily Group B Tab. Metformin 500mg thrice daily

*P value determined by chi-square test

After 6 months, the incidence of vomiting, generalised weakness, and flatulence was observed more with metformin (group B), and this difference was statistically significant (p<0.05).

Discussion

This study was carried out at Rajshahi Medical College Hospital, Rajshahi, from April 2021 to March 2022 in the Department of Gynecology & Obstetrics. The patients attending the OPD of the Gynecology & Obstetrics department, with PCOS, were selected. It was a randomised controlled trial with a sample size of 100. Among them, 50 Participants enrolled in group A (experimental group) who received tab. Myo-inositol 1g twice daily for 6 months. Another 50 patients were enrolled in group B (control group), treated with a tablet. Metformin 500 mg thrice daily for 6 months. Patients were called for follow-up after 3 months and 6 months of drug therapy, and tests for all the study variables were repeated and compared with the baseline findings. In all, 100 patients were enrolled for the study within the age 18 to 33 years. Since the age distribution of patients was from 18 to 33 years, the study covers the mean population age of 24.22±3.27 years in total. Among group A, the mean age was 24.20±3.09 years and group B 24.24±3.47 years, with statistically similar between groups (p=0.856). It is similar to studies conducted by Immediata et al. and Costantino et al., and Tagliaferri et al [10,11].

The majority of participants with PCOS in the study were between 21-25 years of age (59.0%), followed by 27.0% in 26-30 years. That means about 86.0% participants were between 21-30 years of age. It was reported in a previous Bangladeshi study that the mean age was 23.55 years, while 72.7% were within the age of 20-29 years for PCOS patients [8]. Another study showed a mean age of 24.36 years, with the majority in the 21-30 years of age (75.3%) [12]. In the current study, the maximum number of women (70.0%) came from urban areas for treatment, whereas 30.0% women came from rural areas. A Bangladeshi study showed 64.2% women hailed from urban areas [12]. It was noted that 11.0%, 24.0%, 43.0% and 22.0% women were illiterate, primary, secondary and higher secondary level of education, respectively. About 71.0% women were homemakers and 17.0% in service. Almost the same results were found in Hussein and Alalaf's [13] study; they reported that most of the infertile women (84%) in Turkey were housewives, and a remarkable number of women (27.4%) were higher educated [13].

The family income of 60.0% participants was middle class, ranging from 20001 to 40000 BDT, followed by 35.0% had ≤20000 BDT, and the remaining 10.0% had >40000 BDT. In a study conducted in Malaysia, researchers found that 47.9% infertile Malaysian women were living in middle-income families [14]. Researchers have shown that lower and middle socioeconomic classes have increased PCOS rates due to stress related to financial hardships and treatment, poor nutritional diet, lack of knowledge, lack of understanding between couples and family members regarding fertility issues, poor quality of life and impaired health due to unhealthy lifestyle habits [15,16,17].

The mean baseline weight of group A and group B patients in the study was 62.38±2.65 Kg and 61.77±4.49 Kg, respectively. There was no intergroup association regarding baseline weight (p=0.415). But there was a statistically significant reduction in weight at the end of 3 and 6 months compared to baseline values in both groups (p<0.001). BMI in the metformin group was reduced from a mean of 26.58±3.14 to 25.89±2.89 after 3 months and 25.18±2.65 after 6 months of treatment, which is highly significant compared to baseline (p<0.001) in the MI group. Similar results were seen in studies done by Le Donne et al. and Cheang et al. Cheang et al [18,19].

Immediata et al. conducted a crossover study in which metformin was able to decrease body weight ($p < 0.05$) but did not observe during MI administration, which is not in concordance with our study [11]. In study, at baseline, 20% group A patients and 24% group B patients had regular menstrual cycles, which improved up to 34% at 3 months, 58% at 6 months in group A and 36% at 3 months and 50% at 6 months in group B. However, difference between two groups was not statistically significant (p>0.05). This is similar to findings obtained by Leo et al and Maria Concetta Musacchio [20,21]. Nabi and Guleria studied that, after treatment, in patients taking MI 2gm daily, 53.1% of patients achieved regular cycles whilst in patients taking metformin 500 mg twice daily, 41.9% of patients achieved regular cycles [22]. Previous studies stated that taking MI 2 gm twice daily causes improvement of menstrual cycle in 88.0% by Papaleo et al. Some other authors showed that taking MI 1gm per day causes 66.66% improvement of menstrual cycle while taking 1gm twice daily causes 74.65% improvement [23,24]. Moreover, taking metformin 500 mg thrice daily causes a 67.0% improvement in menstrual cycle [25,26]. The Ferriman-Gallwey score (FG score) to determine hirsutism status was assessed at baseline, after 3 and 6 months of treatment. Mean FG score was statistically similar between groups at baseline (11.18±5.01 vs 11.62±6.73; p=0.712). After 3 months of treatment with MI and metformin, mean FG score decreased and it was 8.70±5.04 and 10.28±6.18, respectively. This finding was also non-significant. After consecutive treatment of 6 months, group A value decreased up to 5.52±4.25 and group B value up to 9.0±5.38, which is significant between groups (p<0.001). Comparison of 3 months and 6 months FG score for both groups with baseline showed significant changes (p<0.001). In a study done by Leo et al, 60 insulin-resistant PCOS patients were randomly assigned to three groups. All groups were treated for 6 months with MI (1500 mg BD) and monacolin K (3000 mg BD), or inositol only (1500 mg BD), or metformin only (850 mg BD). Following 6 months of treatment, there was a reduction of 2.0 in m FG score with both drugs [20]. Nabi and Guleria also showed a significant decrease in hirsutism score before and after treatment in both MI and metformin groups [22]. The mean plasma FSH (follicle-stimulating hormone) between group A and group B showed no significant difference.

Comparison of FSH and LH with baseline values at the end of 3 months and 6 months showed significant changes in both groups. A marked decrease in LH plasma levels was obtained in metformin-treated patients, reaching statistical significance [26]. Among group A patients, 32% had acne before treatment, which was improved after 3 months of treatment (16.0%). After 6 months, only 8% had acne in group A, which is significantly less than group B after 6 months (22.0%); p=0.021. Zacche M et al observed a comparable improvement of 53% in cases of acne on treatment with Myoinositol for 6 months [27]. Ranwa M et al observed an improvement of only 33.3% in cases of acne in cases of PCOS on administration of 2 gm Myoinositol per day [28]. Common adverse drug reactions among group A patients after 3 months and 6 months are menorrhagia (24% and 22%), Dizziness (10.0% and 8%), nausea (8.0% and 12.0%), etc. Among group B patients, common adverse reactions are, nausea (30.0% and 24.0%), generalized weakness (26.0% and 20.0%), flatulence (22% and 16%), vomiting (16% and 20%), dizziness (12% and 10%), abdominal cramp (10% and 14%) etc. After 3 months of treatment, nausea, vomiting, weakness, and flatulence were significantly more found in patients who took metformin (group B) ($p<0.05$). Also, after 6 months of treatment, vomiting, weakness, and flatulence are significantly more prominent among group B patients ($p<0.05$). Myoinositol (group A) is only significantly associated with menorrhagia both after 3 months and after 6 months of treatment. In a study done by Angik et al, in which metformin and MI were compared to observe for their safety, a total of 36 out of 50 patients experienced the side effects of treatment with metformin [3]. 2% patients had lactic acidosis, 38% generalised weakness, 32% had nausea, and 28% did not have any side effects where whereas 84 % patients in the myoinositol group did not experience any side effects, but 14% had menorrhagia and 2% had nausea. In the myoinositol group, only 16% patients experienced side effects in contrast to 72% in the metformin group, with a p value of <0.0001, which was statistically significant [3]. In a study done by Carlomagno and Unfer, in which the authors studied the safety of the MI and reported that the highest dose of MI (12 gm/day) induced mild GI side effects, nausea, flatus and diarrhoea. The severity of side effects did not increase with the dosage [29,30].

Limitations

1. All samples were collected from a single site
2. The sample size was small
3. Long-term follow-up was beyond scope of study
4. It was not possible to complete the whole sample size due to time constraints, which would rather given a more accurate result.

Conclusion

This open-label randomised control trial observed that myo-inositol is comparably effective and has a better safety profile than metformin in the treatment of PCOS patients. Several conclusions were confirmed by our findings. First, we found that the average Ferriman-Gallwey score and Luteinizing hormone were lower in the myo-inositol group than in the metformin group at the end of 6 months. Second, acne was reduced more in the myo-inositol group than metformin group. However, both groups had a significant improvement in their regular menstrual cycle. Third, after six months, menorrhagia, dizziness and nausea were the major adverse drug reactions (ADRs) in the myo-inositol group, while nausea, vomiting, weakness, abdominal cramps, and flatulence were the major ADRs in the metformin group. Moreover, vomiting, generalised weakness, and flatulence were significantly higher in the metformin group than myo-inositol group. Thus, Myo-inositol is a safe and secure drug with better patient compliance, which in turn leads to better therapeutic outcomes in PCOS patients. These results correspond with the findings of other similar studies with slight variations. However, further study with a larger sample size and longer follow-up is recommended.

Recommendation: Further multicenter studies with larger sample sizes and longer follow-ups are recommended.

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- **Conflict of interest:** None Initiated

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