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ORIGINAL ARTICLE

Comparison of metformin plus myoinositol vs metformin alone in PCOS women undergoing ovulation induction cycles: randomized controlled trial

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ABSTRACT

The present study was planned to evaluate the benefit of synergetic effect of Metformin plus Myo-inositol versus Metformin alone in infertile polycystic ovarian syndrome (PCOS) women undergoing ovulation induction. One hundred and twenty infertile PCOS women were randomized: Group I ($n = 60$) received Metformin (500 mg) plus Myoinositol(600 mg) three times a day; Group II received Metformin 500 mg three times a day. Subjects were advised to try for spontaneous conception. Those who did not conceive after 3 months, were given three cycles of ovulation induction + intrauterine insemination. Hormonal and biochemical profile parameters were done at baseline and after 3 months of therapy. Primary outcome measure was live birth rate. Secondary outcomes were improvement in menstrual cycle, hormonal and biochemical parameters, spontaneous conception, abortions, multiple pregnancy, and ovarian hyperstimulation syndrome. Baseline demographic, hormonal and biochemical parameters were comparable in two groups. There was a significant improvement in menstrual cycles (cycle length and bleeding days) in Group I as compared to Group II. Improvement in HOMA-IR was significantly higher in Group I ($p = .03$) as compared to Group II after 3 months. Live birth rate was significantly higher in the Group I as compared to Group II [55% (33/60); 26.67% (16/60); $p = .002$]. The study concluded significantly higher live birth rate in women receiving the combination as compared to metformin alone.

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Introduction

Polycystic ovarian syndrome (PCOS) is the most common cause of anovulatory infertility and prevalence among infertile women is 15–20% [1,2]. Hyperinsulinemia due to insulin resistance occurs in approximately 80% of women with PCOS and central obesity, as well as in 30–40% of lean women diagnosed with PCOS [3,4].

Main treatment modalities for anovulatory infertile PCOS women are dietary and lifestyle modifications, oral ovulation induction agents, gonadotropins, laparoscopic ovarian drilling, and insulin sensitizers. Among insulin sensitizers, metformin has been studied most extensively and there is evidence that it may have metabolic and reproductive benefits [5]. Inspite of being used for decades, metformin has not been able to show results in terms of improved live birth rates in infertile PCOS women though there is evidence of improved clinical pregnancy rate when given along with clomiphene (CC) as compared to CC alone [6].

Recent addition to insulin sensitizers are inositols, among which myo-inositol is the most extensively studied. It acts by a membrane-associated sodium-dependent inositol co-transporter GLUT4 as a post-receptor mediator (second messenger) of insulin signal and decreases hyperinsulinemia. Myoinositol improves ovarian function, decreases leutinising hormone/follicle stimulating hormone (LH/FSH) ratio, reduces serum androgens, increases sex hormone binding globulin (SHBG) and decreases serum total and free testosterone [7].

As the two insulin sensitizers act through different mechanisms, these may be combined to act synergistically to improve metabolic and reproductive outcomes simultaneously in infertile PCOS women. Till now there is no study published to evaluate whether the combination of metformin and myo-inositol can act better than metformin alone in infertile PCOS women. The present study was planned to study the effect of combined metformin and myo-inositol as compared to metformin alone in terms of reproductive outcome and improvement in metabolic and hormonal parameters in infertile PCOS women undergoing ovulation induction cycles.

Materials and methods

A randomized controlled trial was conducted at outpatient department of a tertiary referral center between January 2016 and May 2017. The study was started after approval by the Clinical Research Ethics Committee of the institute. A total of 250 infertile PCOS women (according to Rotterdam criteria) attending infertility clinic were screened for the study. Inclusion criteria were: age between 20 and 38 years who failed to conceive for >12 months, BMI <30kg/m^2 and bilateral patent tubes on hysterosalpingography/laparoscopy. According to inclusion and exclusion criteria, 120 patients were finally recruited for the study. Male factor infertility and uncontrolled hypo/hyperthyroidism couples were excluded. All the participants were randomized into two groups according to computer-generated randomization table. Informed written consent was taken from

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the couple after explaining the detailed plan, purpose, and duration of the study in their own language.

After taking detailed history pertaining to PCOS and infertility, detailed physical examination including weight, height, BMI (Kg/m^2), hip circumference (widest part of hip), waist circumference (horizontal to umbilicus), hirsutism scoring, (modified Ferriman Galway (mFG) scoring), Acne scoring, (Global Acne Grading System) and secondary sexual characteristics were recorded.

Baseline investigations included complete blood count, liver function tests and kidney function tests, lipid profile, Blood sugar fasting, fasting serum insulin and HOMA-IR (mmol/L) (Homeostatic Model Assessment of insulin resistance). Hormonal analysis included serum FSH, LH, TSH, Prolactin, Testosterone, SHBG, and AMH (anti-mullerian hormone) done on day 2–3 of the previous menstrual cycle. Antral follicle count for ovarian reserve and ovarian volume was done on day 2–3 of the cycle.

The subjects were randomized into two groups and received the treatment according to the protocol. Group I ($n = 60$) received Metformin 500 mg + Myoinositol 600 mg three times a day for 6 months. Group II ($n = 60$) received Metformin 500 mg three times a day for 6 months. Patients were advised to keep a record of menstrual cycles and weight and were advised to try for natural conception.

All patients were followed up first at 1 month and then at 3 months of drug therapy and then during their ovulation induction cycles. After 3 months of drug therapy, improvement in clinical parameters weight (kg), BMI (kg/m^2) and menstrual cycle length and flow during periods were reassessed. All the biochemical and hormonal parameters were repeated after 3 months of therapy to see the improvement. Those who conceived spontaneously in initial 3 months were documented and were excluded from subsequent analysis. Rest of the patients were continued on the same drug according to group allocated and, in addition, were given ovulation induction. For ovulation induction, tablet Clomiphene citrate 50 mg was started from day 2 to day 6 of the cycle. Transvaginal ultrasound (TVS) was done from day 9 of cycle and patients were followed with serial TVS till a mature follicle (>18 mm) was documented. Highly purified gonadotropins injections at the dose of 75 IU was administered accordingly depending upon the size of follicle from the eighth day of the cycle of OVI and the dose was increased till follicle of 14 mm size documented if the patient did not ovulate in the first cycle. Inj HCG 5000 IU was given when 1–2 follicles of diameter >18 mm were documented. IUI was done about 36 h following ovulation trigger. Urine pregnancy test was done 16 days after IUI. The drug was continued for first 3 months of conception and then stopped, and patients were then followed till delivery. Those with negative urine pregnancy test and inadequate response were recruited for second cycle of OVI with Clomiphene citrate 100 mg maximum dose in addition of gonadotropins if the patient did not ovulate in first cycle till a maximum of three cycles. The maximum dose of gonadotropins used per day was 225 IU. After every successive cycle, patients who conceived were excluded from subsequent analysis. A record of dropouts and premature terminations from the study was maintained.

Primary outcome measure was live birth rate. Secondary outcome included improvement in clinical, metabolic and hormonal parameters after drug therapy, clinical pregnancy rate, incidence of abortions, multiple pregnancies and ovarian hyperstimulation syndrome (OHSS) cases. Data analysis was carried out using STATA version 12.0. The level of significance was accepted when $p < .05$.

Table 1. Baseline demographic and clinical characteristics between two groups.

Characteristics	Group I ($n = 60$)	Group II ($n = 60$)	p Value*
Age (years)	28.35 ± 2.74	28.12 ± 3.34	0.06
BMI (kg/m^2)	27.71 ± 3.60	27.38 ± 3.92	0.69
Duration of infertility (years)	3.75 ± 2.96	4.52 ± 2.66	0.11
Menstrual Cycle length (months)	2.04 ± 0.80	2.15 ± 0.87	0.44
Bleeding per cycle (days)	4.40 ± 1.42	4.83 ± 1.75	0.46

*$p < .05$ is statistically significant.

Results

According to inclusion and exclusion criteria, 120 infertile PCOS women were recruited for the study and were randomized. Group I ($n = 60$) received metformin + myo-inositol and Group II ($n = 60$) received metformin alone. Table 1 shows the baseline demographic and clinical characteristics of the study subjects.

After 3 months, there was a significant improvement in menstrual cycles (both length and bleeding per cycle) in Group I as compared to Group II ($p = .03$ and .01, respectively). Improvement in HOMA-IR was significantly higher in Group I after 3 months of drug treatment as compared to Group II ($p = .03$). Although, the improvement in fasting blood sugar and insulin levels were statistically insignificant, improvement in HOMA-IR could be due to the difference in standard deviation. Spontaneous resumption of menstrual cycle was considered as a sign of ovulation although serum progesterone level was not done in this study. The clinical parameters, that is, BMI, acne score, and modified Ferriman Gallaway score and hormonal parameters improved in both the groups and the levels were comparable after 3 months (Table 2).

The number of patients who conceived spontaneously in initial 3 months was higher in Group I (23.3%, 14/60) as compared to Group II (13.3%, 8/60) but the difference was not statistically significant ($p = .15$).

Rest of the patients were given ovulation induction + IUI. Ovulation/pregnancy was documented in each cycle and those who conceived were excluded from subsequent analysis. Total number of ovulation induction cycles given per group (OVI ± IUI): Group I: 63; Group II: 70. Clinical pregnancy rate after three cycles of ovulation induction was significantly higher in Group I as compared to Group II.

In Group I, the total clinical pregnancy rate was 63.3% and in Group II, it was 33.3%, respectively at the end of 6 months and the difference was statistically significant ($p = .001$). In Group I and Group II, the live birth rate was 55% (33/60) and 26.67% (16/60), respectively and the difference was statistically significant ($p = .002$) (Table 3). The incidence of gestational diabetes and hypertension was comparable among the two study groups. Mean birth weight was 2908.6 ± 329.8 in Group I and 2861.6 ± 393.5 in Group II and the difference was not statistically significant (p values .66).

Total five patients in Group I suffered from OHSS after ovulation induction with clomiphene citrate in three patients and gonadotropins use in two patients. Out of five cases, one case was early onset OHSS due to exogenous HCG trigger and four cases were late onset OHSS due to endogenous HCG due to pregnancy (twins), There was no case of OHSS reported in Group II.

Table 2. Improvement in clinical, hormonal and biochemical parameters.

Parameter	Baseline			After 3 months		
	Group I	Group II	*p* value	Group I	Group II	*p* Value
Clinical parameters						
Body mass index (kg/m^2)	27.71 ± 3.60	27.38 ± 3.92	.69	25.77 ± 3.48	25.45 ± 3.22	.60
Cycle length (months)	2.04 ± 0.80	2.15 ± 0.87	.44	1.13 ± 0.28	1.25 ± 0.36	.03
Bleeding (days)	4.40 ± 1.42	4.83 ± 1.75	.46	4.34 ± 0.64	4.57 ± 0.84	.01
Modified FerrimanGallaway score	12 (0.5–18)	12 (6–15.75)	.854	5.0 (0–8)	5.5 (2–8)	.71
Global acne score	4 (0–8.75)	0 (0–7.75)	.361	0 (0–6)	0 (0–4)	.09
Hormonal parameters						
Sr. LH (mIU/ml)	11.53 ± 5.34	10.32 ± 4.43	.99	7.36 ± 2.88	7.20 ± 2.59	.51
Sr. FSH(mIU/ml)	5.64 ± 1.73	5.51 ± 2.32	.85	5.81 ± 1.09	5.69 ± 2.06	.82
LH/FSH ratio	2.1 ± 0.87	2.03 ± 0.98	.87	1.25 ± 0.40	1.30 ± 0.46	.38
Sr. Testosterone (ng/dl)	0.50 ± 0.16	0.52 ± 0.16	.48	0.36 ± 0.10	0.37 ± 0.10	.75
Sr. SHBG(nmol/L)	10.91 ± 3.21	11.82 ± 3.29	.45	29.76 ± 9.52	28.54 ± 8.64	.41
Sr. AMH (ng/ml)	12.22 ± 5.16	11.23 ± 4.26	0.09	7.91 ± 2.97	7.23 ± 2.23	.10
Biochemical parameters						
Blood sugar fasting (mg/dl)	92.73 ± 9.41	93.75 ± 11.46	0.40	81.725 ± 7.47	83.350 ± 7.80	.92
Blood sugar PP (mg/dl)	118.95 ± 20.79	120.07 ± 26.18	0.10	103.57 ± 15.63	108.18 ± 15.79	.48
Insulin fasting (uIU/dl)	12.03 ± 6.13	12.03 ± 4.39	0.70	7.29 ± 2.57	7.85 ± 2.65	.91
HOMA-IR index	2.78 ± 1.6	2.83 ± 1.29	0.85	1.46 ± 0.51	1.62 ± 0.59	.03
Total cholesterol (mg/dl)	162 ± 25.57	160 ± 34.68	0.164	136.56 ± 21.49	137.79 ± 21.12	.93
LDL(mg/dl)	99.04 ± 21.31	100.40 ± 16.70	0.416	85.59 ± 11.42	84.84 ± 12.17	.93
HDL(mg/dl)	42.52 ± 5.96	41.55 ± 4.86	0.104	48.97 ± 5.21	48.99 ± 5.05	.54

$p < .05$ is statistically significant.

Table 3. Per cycle analysis of ovulation induction cycles between two groups.

Ovulation induction cycle	Parameters	Group I ($n = 60$)	Group II ($n = 60$)	*p* Value
Spontaneous conception		14 (23.3%)	8(13.3%)	.15
First cycle	No of patients	46	52	
	Ovulation rate	16/46 (34.8%)	7/52 (13.5%)	.013
	Conception rate	9/46 (19.6%)	4/52 (7.7%)	.08
Second cycle	No of patients	37	48	
	Ovulation rate	29/37 (78.4%)	29/48 (60.4%)	.07
	Conception rate	13/37 (35.1%)	3/48 (6.2%)	.001
Third cycle	No of patients	24	45	
	Ovulation rate	18/24 (75%)	34/45 (75.6%)	.95
	Conception rate	2/24 (8.3%)	5/45 (11.1%)	.71
Conception after ovulation induction		24/46 (52.17%)	12/52 (23.07%)	.003
Clinical pregnancy rate		38/60 (63.3%)	20/60 (33.3%)	.001

Discussion

The present study shows significantly higher live birth rate in women who received the combination of metformin and myo-inositol as compared to metformin alone.

Though both metformin and myo-inositol are insulin sensitizers, the mechanism of action of the two is different. While metformin is the classical and most frequently used molecule for the treatment of PCOS [8,9], the focus on myo-inositol is comparatively recent [10]. The studies have shown improved metabolic and reproductive functions with myo-inositol without any gastro-intestinal side effects of metformin [11,12].

Fruzzetti et al. compared metformin and myo-inositol for treatment of clinical and metabolic aspects of PCOS. The study concluded that two insulin-sensitizers lower BMI and ameliorate insulin sensitivity and improve menstrual cycle without any significant differences between the two treatments [13]. About 50% of women resumed spontaneous menstrual cycles in this study though serum progesterone levels were not checked. The present study showed improved menstrual cyclicity in both the groups but the improvement was significantly higher in the combination group. Improved ovulation may be the reason for spontaneous menses and higher pregnancy rate in the group who received the combination. The comparable improvement in hormonal and biochemical parameters in two groups of present study may be attributed to metformin which has been labeled to improve metabolic mileu in PCOS women [14].

In a recent Cochrane review, authors have concluded that metformin may increase the live birth rate among women undergoing ovulation induction with gonadotrophins and can be started before giving ovulation induction [15].

Raffone et al. compared the two insulin sensitizers in infertile POCS women. Though the absolute number of women resuming spontaneous ovulation and total conception rate was higher in myo-inositol group, the study failed to show any statistically significant difference between the two groups [16].

In a small three arm study, metformin (1500 mg), myo-inositol (1g/day), or the combination were compared in infertile PCOS women. There was a significantly higher improvement in symptom profile, weight loss, and hormonal parameters in myo-inositol and the combination group. The study concluded that myo-inositol may be used for improving the ovarian function and hormonal parameters in PCOS women [17].

The ideal dose of myo-inositol has not yet been defined. The studies have used 1–4 g per day in different settings [16–18]. As it acts at ovarian level, myo-inositol corrects the insulin resistance and hormonal disturbances at ovarian level thus reducing the dose of gonadotrophins and risk of ovarian hyperstimulation syndrome in PCOS women during ovulation induction and IVF [18,19].

Emekçi Özay et al. compared Myoinositol and folic acid with myoinositol alone in infertile PCOS women and documented significantly higher spontaneous conceptions and clinical pregnancy rate in myo-inositol group. [20].

As myo-inositol has no GI side effects with similar clinical and hormonal benefits as metformin, it may be considered as first line option in PCOS women with insulin resistance without pre-diabetes or diabetes [21].

The inference may be made that the two drugs acting synergistically, have more hormonal, clinical, and reproductive benefits as compared to when one drug is given alone.

Main limitation of the present study was that serum progesterone levels were not checked to document ovulation.

Among metformin and myo-inositol, which molecule is more beneficial is still a debate. But literature is inclining toward more benefits of myo-inositol and choosing it first line option in PCOS women with or without insulin resistance though its ideal dose is yet to be defined. Further randomized controlled trials are needed comparing the two molecules separately with the combination to prove or disprove the benefits of combinations.

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Disclosure statement

No financial relationship with any organization. Authors have full control of all primary data. Informed written consent was obtained from the patients for publication. The authors report no conflicts of interest.

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