International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Angik R et al. Int J Reprod Contracept Obstet Gynecol. 2015 Feb;4(1):189-194
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: 10.5455/2320-1770.ijrcog20150234

Research Article

A comparative study of metabolic and hormonal effects of myoinositol vs. metformin in women with polycystic ovary syndrome: a randomised controlled trial

Riju Angik*, Shubhada S. Jajoo, C. Hariharan, Amogh Chimote

Department of Obstetrics & Gynaecology, Acharya Vinoba Bhave Rural Hospital (AVBRH), DMIMS (DU), Sawangi (Meghe), Wardha, Maharashtra, India

Received: 19 December 2014
Accepted: 11 January 2015

***Correspondence:**
Dr. Riju Angik,
E-mail: riju_angik07@yahoo.com

ABSTRACT

Background: The purpose of the study was to find out which drug is more effective in treatment and improvement of metabolic and hormonal parameters in women with polycystic ovary syndrome (PCOS); Myoinositol or Metformin. This study was conducted since there are very limited studies on the same.
Methods: Patients between 15-40 years of age with signs and symptoms of PCOS who attended the outpatient department of obstetrics and gynaecolgy at AVBRH between study period of September, 2012 to August 2014, were subjected to specific investigations to diagnose PCOS. Patients who were diagnosed with PCOS according to the Rotterdam criteria were included in the study group. Patients were randomly allocated to treatment with either myoinositol or metformin. Myoinositol group received 1 g twice daily while Metformin group received 500 mg twice daily for 6 months .The findings and investigations were repeated after 6 months and was compared with the baseline values.
Results: Treatment with myoinositol and metformin both decreased body mass index, androgenic features, improved menstrual abnormalities and polycystic ovaries but the Level of insulin resistance as measured by fasting insulin and homeostatic model assessment (HOMA) decreased only on treatment with myoinositol.
Conclusions: Myoinositol acts at the level of insulin receptors and is effective in treatment of hyperinsulinemia and insulin resistance, which is the underlying factor leading to the development of polycystic ovary syndrome.

Keywords: Polycystic ovary syndrome (PCOS), Myoinositol, Metformin, Insulin resistance, Homeostatic model assessment (HOMA)

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrinological disorders in women in reproductive age group with estimated incidence of 5-10 % .[1] It is defined as a heterogenous syndrome complex characterized by the presence of hyperandrogenism (clinical and/or biochemical), ovarian dysfunction (oligo/anovulation and/or polycystic ovaries), with the exclusion of related disorders. This is with the recognition that forms of PCOS may occur without overt evidence of hyperandrogenism.[2]

In spite of tremendous scientific interest and research, controversy continues regarding almost all aspects of PCOS. Diagnosis, prevalence, etiology, pathophysiology, management, long-term risks, clinical and biochemical features of these women may vary according to race, ethnicity, and criteria used for diagnosis. Hyperinsulinemia and Insulin Resistance (IR) has proved to be a key link in the generation of the symptoms of

PCOS, that is, anovulatory infertility, menstrual irregularities and skin stigmata induced by hyperandrogenism.

Given the association between PCOS and IR, insulin-sensitizing agents have been used in the therapy of PCOS. The last few decades of research have recognized the central role of insulin in the pathogenesis.

Insulin sensitizing agents increase the tissue sensitivity to insulin action *in vivo* and enhance insulin activity in PCOS women. Metformin, an oral biguanide is commonly being used in clinical practice. It was the first insulin sensitising drug to be used in PCOS to investigate the role of insulin resistance in the pathogenesis of the syndrome. But, the action of metformin is limited due to low levels of inositol in PCOS. This problem leads the researchers to study in depth about the metabolism of glucose and the role of Phosphoinositol-3 kinase (PI 3 kinase). This brings about altered insulin signalling causing hyperinsulinaemia and insulin resistance.

Isoform of inositol belongs to the vitamin B complex. Myo-inositol, which is optically inactive, is the only form of the nine cyclohexanehexols with known biological importance. Free myo-inositol is produced in all eukaryotic cells and is present in all animal tissues. It accelerates the dephosphorylation of glycogen synthase and pyruvate dehydrogenase, both rate-limiting enzymes of nonoxidative and oxidative glucose disposal. Supplying D-chiro inositol or myo-inositol can accelerate glucose disposal and sensitize insulin action. Although D-chiro-inositol was the predominant form studied initially in PCOS, the focus of recent studies has been on myo-inositol which is a precursor to D-chiro-inositol.

Various studies have been done on metformin, D-chiroinositol and myoinositol but there are very limited studies comparing the efficacy of these drugs in treatment of PCOS. In this study, we have compared the metabolic and hormonal effects of myoinositol and metformin in women with polycystic ovary syndrome.

Aim

To compare the metabolic and hormonal effects in patients receiving myoinositol to those receiving metformin.

Objective

1) To study the varied clinical presentation of PCOS.
2) To study the effect of metformin and myoinositol in treatment of infertility.
3) To study the hormonal profile in patients with PCOS in the two groups.
4) To compare the effectiveness of myoinositol and metformin.

METHODS

The study was carried out at Jawaharlal Nehru Medical College and Acharya Vinoba Bhave Rural Hospital, a tertiary health care centre, located in Sawangi, Wardha, Maharashtra for duration of two years from September, 2012 to August, 2014. It was randomized controlled Trial with a sample size of 100.

The patients attending the gynaecology OPD with clinical features suggestive of PCOS (menstrual abnormalities, infertility, obesity, acne, hirsuitism) were selected. They were further subjected to biochemical investigations and ultrasonography to confirm diagnosis. We defined patients as having PCOS according to the Rotterdam criteria .The diagnosis of PCOS was made if the patients had two out of three of the following:

1. Oligo and/or anovulation: Oligomenorrhoea was defined if menses occurred less than nine times a year or if three cycles more than 36 days long occurred during the last year.

2. Clinical and/or biochemical signs of hyperandrogenism: Clinical hyperandrogenism was diagnosed if the modified Ferriman and Gallwey (mFG) score was 8 or greater or the patient had moderate to severe acne, defined by the presence of inflammatory lesions and their extension.

3. Polycystic ovaries (by ultrasound): Presence of 12 or more follicles in each ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume (>10 mL; calculated using the formula 0.5 x length x width x thickness). Even ovary fitting this definition was enough to define PCOS.

Inclusion criteria

All the females of age group 15-40 years attending OPD of Obstetrics and Gynaecology at AVBRH fulfilling the Rotterdam criteria.

Exclusion criteria

- Patients already on other drug treatment for PCOS(like oral contraceptive pills)
- Deranged kidney or liver function tests
- Thyroid disorders
- Known hypersensitivity to myoinositol

Treatment modality

Approval was obtained from the ethical committee of the hospital. Patients were randomly allocated to treatment with either myoinositol (50 in myoinositol group) or metformin (50 in metformin group), by means of a computer generated number table, and by using sealed opaque envelopes, numbered and used consecutively. Prior to enrolment, a written informed consent was

obtained from the patient. Women who met the inclusion criteria were subjected to treatment according to the randomisation number. The randomisation list was kept concealed until the study was complete. Baseline levels of the study variables were recorded. Participants of myoinositol group received myoinositol 1 gm twice daily and, of metformin group received 500 mg metformin tablet twice daily. The patients were called for follow up after 6 months of drug therapy and then all the baseline measurements were repeated. The anthropometric, biochemical and ultrasonography findings after 6 months of treatment were compared with the baselines findings in each study group. Infertility patients who conceived after treatment was noted. The side effects experienced in each study group was also noted down. Finally the efficacy of the two drugs, myoinositol and metformin, in improving the metabolic and hormonal parameters in the patients, was compared.

Statistical analysis

The data was analyzed using SPSS version 17 software. The statistical significance was tested at 5% level of significance. For continuous variables students t-test was used. Descriptive statistics were analysed for the data that were quantitative and expressed as mean & Standard Deviation (SD).

Unpaired t-test was used to compare the effect of myoinositol and metformin on the biochemical parameters.

RESULTS

Present study was carried out on 100 patients with PCOS. We used history, clinical examination and investigations as per Rotterdam Consensus-2003 criteria for defining PCOS. In the study group, total 47% patients had regular menstrual cycle and 53% had irregular cycle. Out of 53 patients, 15 patients had oligomennorrhoea and 28 presented with secondary amenorrhoea (Table 1).

Overall, after six months of treatment, 20 (37.73%) achieved regular cycles, 28.57% with myoinositol and 48% after metformin treatment (Table 2).

Table 1: Menstrual abnormality.

	Myoinositol	Metformin	Total	P value
Irregular cycles	28	25	53	0.548
Scanty flow	13	12	15	
Secondary amenorrhoea	15	13	28	
Regular cycles	22	25	47	

Table 2: Shows the menstrual cycle of the patient before and after 6 months of treatment.

	M/I		Total	P value
	Myoinositol	Metformin		
Before treatment				
Regular	22	25	47	0.689
Irregular	28	25	53	
Total	50	50	100	
After 6 months of treatment				
Regular	30	37	67	0.002*
Irregular	20	13	33	
Total	50	50	100	

The reduction in the mean modified Ferriman Gallwey score (mFG) of hirsutism and acne was statistically significant in both the groups, but on comparing the two groups, the reduction was not significant.

Similar findings were seen in Body Mass Index (BMI), Waist Hip Ratio (WHR), Fasting Blood Sugar (FBS), Post Meal Blood Sugar (PMBS) and post meal insulin, testosterone, Luteinizing Hormone (LH), LH/FSH ratio, mean ovarian volume and Antral Follicle Count (AFC).

The mean fasting insulin decrease in myoinositol was from 16.51 ± 13.94 to 14.58 ± 9.79, which was statistically significant but in metformin group the reduction was not significant.

Homeostatic model assessment (HOMA) index, an index of insulin resistance. Decreased from mean of 4.21 ± 3.634 with P value of 0.001 in myoinositol group but the decrease was not significant in the metformin group. On comparing the two groups, the decrease in HOMA was significant with P value of 0.004 (Table 3).

Seventy percent patients were married in study group. Out of those seventy married patients, 56.33% had presented with infertility (Table 4).

Out of 19 infertility patients in the myoinositol group, 36.84% conceived and out of 21 patients in metformin group, 33.33%. The results in the two groups were comparable but it was not significant statistically.

Total 36 out of 50 patients experienced the side effects of treatment with metformin. 2% patient had lactic acidosis, 38% generalized weakness, 32% had nausea and 28% did not have any side effects where as 84 % patients in the myoinositol group did not experience any side effect but 14% had menorrhagia and 2% had nausea. In the myoinositol group only 16% patients experienced side effect in contrast to 72% in the metformin group with a P value of <0.0001 which was statistically significant (Figure 1).

Table 3: Comparison of improvement in various clinical, biochemical and ultrasonography parameters before and after treatment in the two groups.

	Myoinositol (I)			Metformin (M)			I vs. M
Variables	**Mean ± SD**	**Mean ± SD**	**P value**	**Mean ± SD**	**Mean ± SD**	**P value**	**P value**
BMI	24.10 ± 4.13	23.97 ± 3.02	0.001*	23.23 ± 2.65	23.22 ± 3.51	0.001*	0.987
WAIST	73.43 ± 9.23	76.14 ± 7.41	0.071*	72.10 ± 9.18	71.36 ± 8.86	0.002*	0.683*
WHR	0.79 ± 0.10	0.80 ± 0.07	0.088	0.79 ± 0.08	0.76 ± 0.06	0.396	0.031
mFG score	10.24 ± 2.08	10.67 ± 2.82	0.001*	8.47 ± 1.68	8.29 ± 2.37	0.002*	0.813
ACNE	1.56 ± 0.501	1.74 ± 0.443	0.002*	1.48 ± 0.50	1.68 ± 0.47	0.001*	0.513
Ovarian volume	14.45 ± 3.8	12.35 ± 2.83	0.001*	14.53 ± 3.44	12.24 ± 2.83	0.001*	0.840
AFC	11.40 ± 3.00	11.60 ± 2.13	0.001*	10.20 ± 2.31	10.18 ± 2.08	0.001*	0.964
FBS	98.62 ± 20.49	98.16 ± 18.12	0.001*	92.44 ± 11.23	92.34 ± 12.17	0.001*	0.966
PMBS	134.88 ± 17.69	136.14 ± 22.64	0.001*	129.42 ± 15.12	128.24 ± 12.26	0.001*	0.669
Fasting insulin	16.51 ± 13.95	17.03 ± 15.41	0.005*	15.08 ± 9.81	14.58 ± 9.80	0.072	0.799
PM insulin	28.82 ± 18.59	32.69 ± 24.69	0.001*	30.22 ± 22.99	26.46 ± 16.47	0.001*	0.349
HOMA	4.21 ± 3.63	4.32 ± 4.61	0.001*	3.50 ± 2.34	3.39 ± 2.28	0.036	0.004*
S. testosterone	57.21 ± 28.80	58.28 ± 27.36	0.001*	54.68 ± 24.81	52.24 ± 24.77	0.001*	0.624
LH	10.03 ± 7.86	10.00 ± 6.25	0.001*	7.48 ± 5.21	8.30 ± 6.65	0.001*	0.494
LH/FSH	1.91 ± 0.99	1.94 ± 0.79	0.001*	1.52 ± 0.79	1.61 ± 0.84	0.001*	0.999

*Significant

Table 4: Conception after treatment.

	Conception		Total	P value
	Yes	**No**		
Myoinositol	7	12	19	0.921
Metformin	7	14	21	
Total	14	26	40	

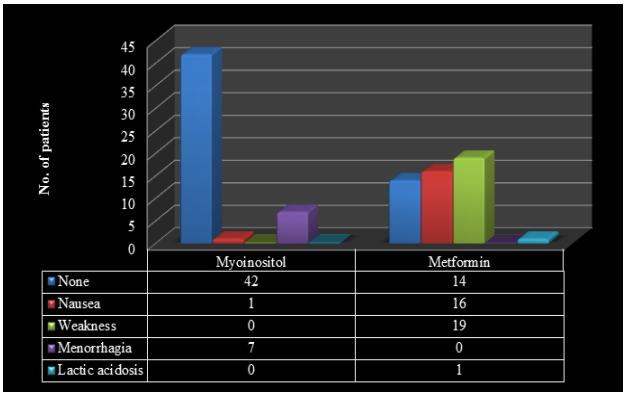

Figure 1: Side effects of the drugs.

DISCUSSION

Vincenzo et al.[4] compared the effect of metformin and myoinositol. Metformin group and myoinositol both showed significant improvement in regularisation of menses and reduction in FG score and BMI, insulin glucose and HOMA, testosterone, LH. But the study failed to establish superiority of one drug over the other.

Similarly Zacche[5] also found significant decrease in acne after treatment with myoinositol.

Cheang et al.[6] performed a study in which, after a mean follow-up of 36.1 months with metformin treatment, improvements were observed for BMI (decrease of - 1.09 ± 3.48 kg/m^2, P = 0.0117). In the present study BMI after treatment decreased from 23.97 ± 3.51 to 23.23 ± 2.65. WHR did not decrease significantly in myoinositol group (Table 3). This was in contrast to study by Constantino et al.[7]

Artini et al.[8] found that, in consideration of baseline fasting insulin levels, myo-inositol treatment induced similar changes in both groups but only patients in myoinositol group demonstrated significant reduction in fasting insulin levels (20.3 ± 1.8 to 12.9 ± 1.8 µU/mL, P <0.00001).

HOMA index, which is a measurement of insulin resistance decreased in myoinositol group significantly but not in metformin group. On comparison between the two group myoinositol had significantly better action in improving the insulin resistance (Table 3). Zacche[5] also found that basal insulin levels and HOMA index significantly decreased after myoinositol treatment.

Artini et al.[8] found that myo-inositol treatment showed significantly lower Testosterone (2.3 nmol/liter vs. 3.4 nmol/liter; 95% CI = 0.07 and 2.1, respectively; P >0.04), similarly to our study. Zacche[5] also showed decrease in testosterone and LH levels after treatment with myoinositol.

No side effects or adverse events were observed in any of the study participants[7] in contrast, side effects were seen in 14% patients in our study (Figure 1) but these side effects were significantly very less than metformin (Figure 1) in which total of 72% patients had side effects

(Figure 1). Artini et al.[8] also found no side effects or adverse events in any of the study participants receiving myoinositol.

The ovarian volume and Antral Follicle Count (AFC) reduced significantly in both metformin and myoinositol group (Table 3). Another study[9] showed a significant reduction in mean ovarian volume (11.70 ± 4.31 ml vs. 8.27 ± 3.71 ml P = 0.001) after three months of treatment with metformin.

Table 5: Comparison of improvement in various clinical, biochemical and ultrasonography parameters before and after treatment in the two groups.

Reference	Study design	Form and dose	Outcomes
Constantino 2009[7]	Double blind placebo controlled trial in 42 women with PCOS	Myoinositol + folic acid versus folic acid + placebo	Significant decrease in free testosterone, systolic and diastolic BP and improvement in insulin sensitivity
Zacche 2009[5]	Prospective trial in 50 patients with PCOS	Myoinositol 4 g + 400 mcg folic acid/d x 6 months	Improvement in acne and hirsuitism. LH, testosterone, basal insulin levels and HOMA index significantly decreased compared to baseline
Vincenzo et al.[4]		Myo-inositol and monacolin K (Group A), inositol only (Group B) and metformin treatment (Group C)	After 6 months of therapy all study groups demonstrated shorter menstrual cycles, lower Ferriman-Gallwey scores and decreased BMI and LH/FSH ratio. Observations, which were probably the consequence of weight loss and improvement in insulinresistance, were associated with inositol intake. The reduction in BMI was more pronounced in group A (myo-inositol + monacolin k), compare to group B (inositol only). Ferriman-Gallwey score, as well as androgen levels were significantly reduced in all study groups, with a tendency toward a better improvement following the combined treatment with myoinositol and monacolin k. While glucose, insulin and HOMA index were significantly decreased in all groups, the HOMA index in patients treated with myoinositol and monacolin k were within the normal range.
Present study	Randomized controlled trial in 100 PCOS (n=50 in myoinositol group and n=50 in metformin group)	Myoinositol 1 gm BD vs. metformin 500 mg bd/d x 6 months	Treatment with myoinositol decreased BMI, FG score, acne, systolic BP, FBS, PMBS, fasting and post meal insulin, HOMA, testosterone, LH/FSH and ovarian volume significantly but not waist circumference, and WHR where as in metformin group metformin significantly improved BMI, waist circumference, FG score, acne, FBS, PMBS, PM insulin, serum testosterone, LH, LH/FSH and ovarian volume but not WHR, fasting insulin, HOMA. Conception occurred in 36.84% with myoinositol, and 33.33% with metformin.

CONCLUSION

Aim of our study was to compare the metabolic and hormonal effects of a chronic treatment with myoinositol versus metformin in PCOS patients. Using a comprehensive, detailed endocrinological and clinical assessment, we have shown that myoinositol and metformin, both the drugs resulted in significant weight loss, regularisation of menses and improvement in endocrinological parameters. In women with the PCOS, insulin resistance is related to a deficiency in myo-inositol containing mediator of insulin action and the administration of the myo-inositol improves insulin sensitivity to conclude, metformin is effective in reducing the metabolic and hormonal parameters and also improves fertility but myoinositol not only improves all the above parameters but also decreases insulin resistance.

Myoinositol also has better patient compliance and well tolerated than metformin. These beneficial effects of inositol support a future therapeutic role in women with PCOS. Inositol deficiency is the basic pathophysiology for PCOS, hence inositol supplementation is essential in the management of PCOS to improve insulin sensitivity.

PCOS is not only a health hazard but also an economic burden. Based on the above observations it can be said

that, since the clinical features of PCOS are heterogeneous, they have to be investigated accordingly, for selection of appropriate treatment modality. Early identification of high risk cases and timely therapeutic intervention can halt this on-going process and prevent long term complications.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. Asuncion M, Calvo RM, San Millan JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab. 2000;85:2434-8.
2. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Task force on the phenotype of the polycystic ovary syndrome of the androgen excess and PCOS society. The androgen excess and PCOS society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril. 2009;91:456-88.
3. Fauser B, Taratzis B, Chang J, Aziz R. ESHRE/ASRM-Consensus document on polycystic ovary syndrome. Fertil Steril. 2004;18:19-25.
4. Vincenzo De Leo, Maria Concetta Musacchio, Valentina Cappelli, Alessandra Di Sabatino, Claudia Tosti, Paola Piomboni Leo, et al. A combined treatment with myo-inositol and monacolin k improve the androgen and lipid profiles of insulin-resistant PCOS patients. J Metabolic Synd. 2013;2:2.
5. Zacchè MM, Caputo L, Filippis S, Zacche G, Dindelli M, Ferrari A. Efficacy of myo-inositol in the treatment of cutaneous disorders in young women with polycystic ovary syndrome. Gynaecol Endocrinol. 2009 Aug;25(8):508-13.
6. Kai I. Cheang, Jessica M. Huszar, Al M. Best, Susmeeta Sharma, Paulina A. Essah, John E. Long-term effect of metformin on metabolic parameters in the polycystic ovary syndrome. Nestler Diab Vasc Dis Res. 2009 Apr;6(2):110-9.
7. Costantino D, Minozzi G, Minozzi E, Guaraldi C. Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. Eur Rev Med Pharmacol Sci. 2009;13:105-10.
8. Artini PG, Di Berardino OM, Papini F, Genazzani AD, Simi G, Ruggiero M, et al. Endocrine and clinical effects of myo-inositol administration in polycystic ovary syndrome. A randomized study. Gynaecol Endocrinol. 2013 Apr;29(4):375-9.
9. Marzieh Farimani Sanoee, Nosrat Neghab, Soghra Rabiee, Iraj Amiri. Metformin therapy decreases hyperandrogenism and ovarian volume in women with polycystic ovary syndrome. Iran J Med Sci. 2011 Jun;36(2):90-5.

DOI: 10.5455/2320-1770.ijrcog20150234
Cite this article as: Angik R, Jajoo SS, Hariharan C, Chimote A. A comparative study of metabolic and hormonal effects of myoinositol vs. metformin in women with polycystic ovary syndrome: a randomised controlled trial. Int J Reprod Contracept Obstet Gynecol 2015;4:189-94.