Randomised controlled trial to study the efficacy of exercise with and without metformin on women with polycystic ovary syndrome

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ABSTRACT

Objectives: 1. To study the efficacy of exercise in improving clinical symptoms, anthropometry, glucose tolerance and laboratory profile in women with Polycystic ovarian syndrome. 2. To study the combined efficacy of exercise and metformin on above parameters in women with polycystic ovary syndrome.
Study design: A Randomised double blinded placebo controlled trial was performed at a district hospital in New Delhi. Sixty six women were included in the study. Block randomisation was done to divide the women into two groups. Women were treated with fixed exercise schedule along with oral placebo in Group A and exercise with oral metformin in Group B. Outcomes stated in objectives were studied and statistically analysed. Quantitative variables were compared using unpaired *t*-test and Paired *t*-test within the groups across follow-ups. Qualitative variable has been compared using Chi-Square test /Fisher's exact test.
Results: In Group A and B significant improvement was noted in menstrual cycles, mean waist circumference, mean waist-hip ratio and body mass index. The mean weight loss was 0.78 ± 0.19 kg and 1.71 ± 0.19 kg in group A and B respectively after 3 months. The mean weight loss was 1.08 ± 0.30 kg and 1.71 ± 0.19 kg in group A and B respectively. The mean difference in modified Ferriman Gallwey score at 0, 3 and 6 months were statistically significant in both groups. On comparing group A with group B at 6 months, significant improvement was found in menstrual cycle symptoms (55.17% vs 83.33%), mean weight loss (1.08 kg vs 2.5 kg), waist circumference reduction (2.56 cm vs 4.75 cm) and change in mean waist hip ratio (0.02 vs 0.04). Significant changes were noted in OGTT and Serum testosterone level at 6 months in Group B, but not in Group A. Statistically no significant differences were found in acne, acanthosis nigricans and other biochemical parameters.
Conclusion: Regular exercise should be recommended for the women with PCOS. It results in statistically significant improvement in menstrual cycle pattern, hirsutism, body mass index, weight, waist circumference waist-hip ratio. Addition of metformin resulted in added benefits on menstrual cycle, hirsutism, weight, body mass index, waist circumference, waist hip ratio, serum testosterone and Oral Glucose Tolerance Test (OGTT).

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Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous disorder of multifactorial aetiology with a prevalence of 5%–10% among women of reproductive age [1]. Although the exact etiopathogenesis of PCOS is not known, hormonal imbalance created by hyperandrogenism and insulin resistance is one of the widely accepted and modifiable cause. Traditionally the emphasis has been on symptomatic treatment. Recent emphasis is on improving the insulin resistance resulting in improvement in hyperandrogenism, which helps in improving the long term effects of the disorder. The options for improving insulin resistance range from lifestyle intervention to specific pharmacological agents. Exercise with or without weight loss can lead to a significant reduction in visceral fat and an improvement in insulin sensitivity [2–4]. Insulin sensitisers like metformin have been seen to improve insulin resistance, hyperandrogenemia, anovulation, and acne in PCOS irrespective of pre-treatment insulin resistance and obesity [5]. Exercise and insulin sensitizers are thus often advised for these women. We did this study to find out the usefulness of exercise in these women with PCOS as an independent intervention and also in combination with metformin.

Materials and methods

This randomised double blinded placebo controlled trial was carried out in a district hospital in Delhi over a period of one year.

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The hospital scientific and ethical committee approval was sought before the study (approval letter NO.F (59)/2013/BSAH/DNB/committees/30633). Women attending the outpatient department were screened and included in the study if they fulfilled the eligibility criteria after excluding other diseases like adrenal hyperplasia, cushing syndrome etc. An informed written consent was taken from all women.

Objectives

1. To study the efficacy of exercise on symptoms, anthropometry, insulin sensitivity and laboratory profile in women with PCOS.
2. To study the combined efficacy of metformin and exercise on above mentioned parameters in women with PCOS.

Sample size

Sample size calculation was based on the study "A randomized, 48-week, placebo controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome [6]: The minimum required sample size with 80% power of study and 5% level of significance was calculated as 33 in each group.

Eligibility criteria

Women diagnosed as PCOS on the basis of the Rotterdam criteria [7], willing to participate in the study, follow the exercise schedule and not on any regular exercise regime were included in the study. Exclusion criteria were medical illness contraindicating exercise, untreated hypothyroidism, untreated hyperprolactinemia, smoker, receiving hormones that affects insulin metabolism, received metformin in 3 months prior to study, renal and hepatic disorders.

Randomisation and double blinding

After thorough history and examination women included in the study were divided into two groups by block randomisation with sealed envelope system. Sister-in-charge of Outpatient Department prepared eleven large envelopes each containing six smaller envelopes, three each of group A and B. All selected women were divided into groups of six, depending upon their time of selection. Each time one big envelope was opened and smaller envelopes were randomly chosen by women according to which their group was assigned. Those labelled "A" received placebo along with exercise and those labelled "B" received metformin with exercise. The sister-in-charge kept the record as to which patient belonged to which group and gave metformin/placebo as per the randomisation, such that till the end of the study neither the patients nor the investigator had any knowledge regarding who belonged to which group, thus making the study double blind. At the end of the study group distribution was collected from sister-in-charge and analysed.

Intervention

All women were advised to do marching at the same place for 30 min three days a week for 3 months in the department under supervision. The exercise was monitored by the investigator to ensure a heart rate $\geq$120 beats/min. For the next 3 months all women continued the exercise at home without supervision. Women were given half tablet twice a day for three days and then to one tablet twice a day to reduce the side effects. Each woman was asked to report any side-effect during the treatment. Haematology, liver and renal function tests were assessed before intervention, then at 3-months and 6 months.

Tablet metformin was given in a dose of 850 mg twice a day and Placebo administration was matched in identical doses & tablet shape.

Outcome

Outcome measures were improvement in the clinical symptoms of oligomenorrhoea, polymenorrhoea and secondary amenorrhoea as defined below. Cycles were assessed in previous six months and compared with six months of study period.

Oligomenorrhoea- An average cycle length between 35 and 180 days.

Secondary amenorrhea- The absence of menstruation for 180 days or more.

Polymenorrhoea- An average cycle length $\leq$21 days.

Reduction of acne, acanthosis nigricans and hirsutism (Modified Ferriman-Gallwey score) were assessed by there presence or absence in past 6 months and then compared with their existence during 6 months of treatment. Anthropometric parameters like body weight, body mass index, waist circumference (Normal<80 cm), waist-hip ratio (Normal<0.85) and biochemical parameters like OGTT(Normal F-126, 2-hour level <200 mg/dl), lipid profile including serum triglyceride (Normal<150 mg/dl), serum total cholesterol level (Normal<200 mg/dl), HDL (Normal>40 mg/dl) and Serum total testosterone level (Normal = 15–70 ng/dl) as assessed at 3 months and 6 months of the study. We obtained total serum testosterone (TT) level of only those women with mFG Score was more than 8.

Serum Testosterone was measured using chemiluminescence immunoasssay using architect analyser, laboratory reference ranges: 1.5–7.0 ng/ml for adult females; the intra-essay coefficient of variation was 4.0% and inter-essay coefficient of variation was towards linear regression.

Statistical analysis

We compared various clinical, anthropometric and biochemical parameters within group A and B at 0, 3 and 6 months. Comparative analysis was also done amongst the two groups. Categorical variables are presented in numbers and percentage (%). Continuous variables are presented as mean $\pm$ SD and median. Quantitative variables were compared using unpaired t-test between the two groups and Paired t-test/ Wilcoxan test within the groups across follow-ups. Qualitative variable were compared using Chi-Square test/Fisher's exact test. The data was analyzed with Statistical Package for Social Sciences version 21.0.

Results

We studied 66 women with PCOS divided into group A and B of 33 women each. The two groups showed no significant differences with respect to age, blood pressure, weight, calorie intake etc. at the beginning of the study as shown in Table 1. Calorie intake was measured by 24 h recall method. We didn't intervene actively with calorie intake.

In the study, 54.55% women were obese, 13.64% were overweight and 31.82% women were of normal weight. In group A and B, 21 and 15 women were obese and 4 & 5 were overweight respectively. On comparison the difference was not significant with p Value (0.316).

The parameters studied in Group A are depicted in Table 2. There was significant improvement in the menstrual cycles at 3 months but no statistically significant difference was reported between 3 months and 6 months. Out of 29 (87.88%) women with abnormal menstruation, improvements were reported by 9 women at 3 months and additional 7 women after 6 months.

Table 1
Comparison of characteristics between two groups at 0 months.

Parameters	Group A(n = 33) Mean ± SD	Group B(n = 33) Mean ± SD	P value
Age (years)	24.46 ± 4.76	24.33 ± 3.89	0.91
Calorie Intake (K cal)	1958.21 ± 230.41	1884.82 ± 134.92	0.119
Protein Intake (gms)	47.24 ± 4.59	46.42 ± 4.46	0.478
Systolic Blood Pressure (mm Hg)	117.15 ± 7.19	115.94 ± 8.45	0.625
Diastolic Blood Pressure (mm Hg)	68.73 ± 8.04	66.06 ± 6.6	0.187
Weight (kgs)	60.92 ± 9.13	57.65 ± 10.56	0.154
Height (cms)	152.42 ± 6.23	151.23 ± 5.5	0.260
Modified Ferriman Gallwey Score	4.67 ± 3.43	5.09 ± 3.43	0.537
Body Mass Index	26.32 ± 3.68	25.23 ± 4.64	0.293
Waist Hip Ratio	0.85 ± 0.04	0.84 ± 0.05	0.294
Waist Circumference (cms)	87.39 ± 7.65	85.42 ± 6.7	0.117
Serum Testosterone (ng/dl)	Group A(n = 12)	Group B(n = 12)	P value
Mean ± SD	50.18 ± 18.72	52.27 ± 14.24	0.525

Table 2
Comparison Of Characteristics within group A (33 women).

Parameters	At 0 months	At 3 months	At 6 months	P- value 0 vs 3 months	P- value 0 vs 6 months	P-value 3 vs 6 months
Clinical Parameters	n (%)	n (%)	n (%)			
Oligomenorrhoea	24(72.72%)	17(51.51%)	11(33.33%)	}0.023	0.0001	0.085
Amenorrhoea	3(9.09%)	2(6.06%)	2(6.06%)			
Polymenorrhoea	2(6.06%)	1(3.03%)	0(0.00%)			
Acanthosis nigricans	7(21.21%)	7(21.21%)	3(9.09%)	1.000	0.303	0.303
Acne	8(24.24%)	8(24.24%)	8(24.24%)	1.000	1.000	1.000
Androgenic Parameters	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**			
Modified Ferriman Gallwey Score	4.67 ± 3.43	4.33 ± 3.3	4 ± 3.34	0.008	0.005	0.034
Serum Testosterone (ng/dl)	50.18 ± 18.72	47.3 ± 15.58	44.32 ± 12.51	0.182	0.203	0.155
Anthropometric Parameters	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**			
Body Mass Index	26.32 ± 3.68	25.99 ± 3.63	25.86 ± 3.59	<.0001	<.0001	0.007
Waist Circumference (cms)	87.39 ± 7.65	85.54 ± 7.01	84.83 ± 6.95	<.0001	<.0001	<.0001
Waist Hip Ratio	0.85 ± 0.04	0.84 ± 0.04	0.83 ± 0.04	0.0001	<.0001	0.001
Biochemical Parameters	**n (%)**	**n (%)**	**n (%)**			
OGTT	4(12.12%)	1(3.03%)	2(6.06%)	0.355	0.672	1.000
Serum Triglyceride	3(9.09%)	2(6.06%)	2(6.06%)	1.000	1.000	1.000
Serum cholesterol	11(33.33%)	10(30.30%)	3(9.09%)	0.792	0.033	0.061

No significant improvement was noted in acanthosis nigricans and acne.

On assessment of anthropometric parameters in Group-A, the mean weight loss was 0.78 ± 0.19 kg after 3 months and 1.08 ± 0.30 kg after 6 months and mean BMI improved significantly at both 3 and 6 months. The mean waist circumference reduced by about 2 cm at 3 months and further by about 1 cm at 6 months. The mean waist hip ratio also improved at 6 months. All changes were statistically significant.

The mean difference in modified Ferriman-Gallwey (mFG) score between 0 and 3 months was −0.31 with p-value = 0.008, and between 0 and 6 months was −0.67 with p-value = 0.005. The change in total serum testosterone levels at 3 and 6 months were not statistically significant. The indirect assessment of insulin resistance as done by oral glucose tolerance test (OGTT) showed no significant improvement although two out of four women showed improvement at 6 months. Similarly no significant change was noted in triglycerides level or serum cholesterol level at 6 months.

The changes observed at 3 and 6 months in Group B are depicted in Table 3. Significant improvement was seen in menstrual cycle at 3 months and at 6 months. Out of 24 (72.72%) women who had abnormal menstruation, 9 women reported improvement after 3 months, and an additional 11 women reported improvement after 6 months. No significant

improvement was noted in acanthosis nigricans and acne. The mean weight loss was 1.71 ± 0.19 kg after 3 months and 2.5 kg ± 0.30 after 6 months and thus significant improvement in BMI at 3 and 6 months. The mean waist circumference reduced by about 3 cm at 3 months and further by about 2 cm at 6 months. The mean waist hip ratio at 6 months improved from 0.84 ± 0.05 to 0.8 ± 0.05. All improvements were statistically significant.

The mean difference in mFG score in group B, between 0 and 3 months was −0.85 with p-value = 0.003 and between 0 and 6 months was −1.63 with p-value = 0.0001. No significant change was noted in total testosterone levels at 3 months but at 6 months significant improvement was noted. Out of 6 women with deranged OGTT, 5 improved after 3 months and all after 6 months which was significant. No significant change was noted in triglycerides level and serum cholesterol level. We did not find any women with deranged HDL level at any point of time.

Table 4 compares the various parameters recorded at 6 months in two groups. There was significant improvement in menstrual cycle in group B (83.33%) over group A (55.17%). The mean weight loss was significantly higher in group B (2.5 Kgs) as compared to group A (1.08 kg) but this did not translate into a significant difference in the BMI in two groups. The change in mean waist circumference was significantly more in group B (4.75 cm) in contrast to Group A (2.56 cm). The mean waist hip ratio was

Table 3
Comparison of characteristics within Group B (33 women).

Parameters	At 0 months	At 3 months	At 6 months	P- Value 0 vs 3 months	P- value 0 vs 6 months	P-value 3 vs 6 months
Clinical Parameters	**n (%)**	**n (%)**	**n (%)**			
Oligomenorrhoea	23(69.69%)	15(45.45%)	4(12.12%)	}0.024	<0.001	0.006
Amenorrhoea	1(3.03%)	0(0.00%)	0(0.00%)			
Polymenorrhoea	0(0.00%)	0(0.00%)	0(0.00%)			
Acanthosis nigricans	4(12.12%)	4(12.12%)	3(9.09%)	1.000	1.000	1.000
Acne	6(18.18%)	6(18.18%)	3(9.09%)	1.000	0.475	0.475
Androgenic Parameters	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**			
Modified Ferriman Gallwey Score	5.09 ± 3.43	4.24 ± 2.91	3.46 ± 2.66	0.0003	0.0001	0.0013
Serum Testosterone (ng/dl)	52.27 ± 14.24	47.33 ± 15.48	43.4 ± 13.48	0.0630	0.0430	1.0000
Anthropometric Parameters	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**			
Body Mass Index	25.23 ± 4.64	24.53 ± 4.54	24.16 ± 4.37	<.0001	<.0001	<.0001
Waist Circumference (cms)	85.42 ± 6.7	82.74 ± 6.08	80.67 ± 5.43	<.0001	<.0001	<.0001
Waist Hip Ratio	0.84 ± 0.05	0.81 ± 0.05	0.8 ± 0.05	0.0001	<.0001	0.0003
Biochemical Parameters	**n (%)**	**n (%)**	**n (%)**			
OGTT	6(18.18%)	1(3.03%)	0(0.00%)	0.105	0.024	1.000
Serum Triglyceride	6(18.18%)	5(15.15%)	4(12.12%)	1.00	0.73	1.00
Serum Cholesterol	7(21.21%)	4(12.12%)	1(3.03%)	0.511	0.054	0.355

Table 4
Comparison of characteristics between Groups after 6 months.

Parameters	Group A(n = 33)	Group B(n = 33)	
Clinical Parameters	**n (%)**	**n (%)**	**P value**
Oligomenorrhoea	13 (39.39%)	4 (12.12%)	0.023
Amenorrhoea			
Polymenorrhoea			
Acanthosis Nigricans	3 (9.09%)	3 (9.09%)	1.000
Acne	8 (24.24%)	3 (9.09%)	0.185
Anthropometric Parameters	**Mean ± S.D**	**Mean ± S.D**	**P value**
Weight (kgs)	59.84 ± 8.83	55.12 ± 9.88	0.043
Body Mass Index	25.86 ± 3.59	24.16 ± 4.37	0.090
Waist Circumference (cms)	84.83 ± 6.95	80.67 ± 5.43	0.003
Waist Hip Ratio	0.83 ± 0.04	0.8 ± 0.05	0.008
Androgenic Parameters	**Mean ± S.D**	**Mean ± S.D**	**P value**
Modified Ferriman Gallwey Score	4.0 ± 3.34	3.46 ± 2.66	0.567
Serum Testosterone (ng/dl)	44.32 ± 12.51	43.4 ± 13.48	0.951
Biochemical Parameters	**n (%)**	**n (%)**	**P value**
OGTT	2 (6.06%)	0 (0.00%)	0.492
Serum Triglycerides	2 (6.06%)	0 (0.00%)	0.492
Serum Cholesterol	3 (9.09%)	1 (3.03%)	0.613

P value at baseline =0.215 (insignifiant)

P value at 6 months =0.023 (significant)

Fig. 1. Change in menstrual pattern in two groups.

P value at baseline =0.293 (insignifiant)

P value at 6 months =0.090 (significant)

Fig. 2. Change in BMI in two groups. .

significantly improved in group B when compared with Group A (0.04 vs 0.02). No statistically significant difference was found in acne and acanthosis nigricans and biochemical parameters.

Over the study duration of six months, comparison of two groups showed improvement in menstrual pattern (Fig. 1), BMI (Fig. 2) and reduction in mean waist circumference (Fig. 3).

In group B, 5 (15.15%) women experienced nausea and 4 women (12.12%) complained of vomiting which could be managed with antiemetics easily. All women complied well with little motivation and foreseen positive outcomes. Two women dropped out from each group after 1–2 months as one became pregnant and other 3 did not want to come for supervised exercise, they were not included in the analysis.

Discussion

PCOS is a multifactorial disorder which is problematic not only because of the symptoms but because of its long term impact on women 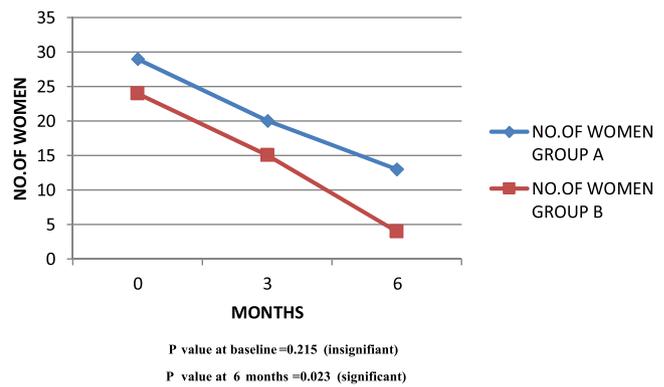health. It is now more frequently encountered in clin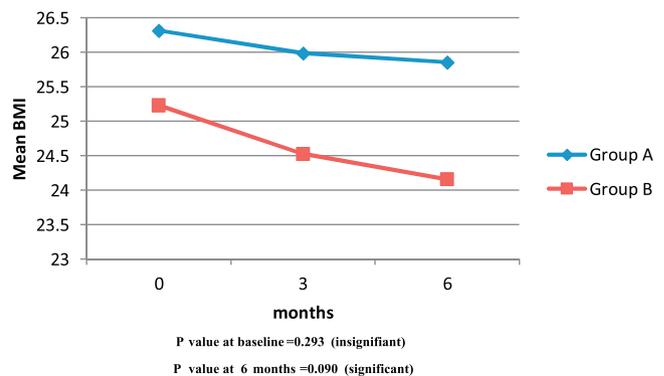ical practice. The treatment perspective has thus shifted from symptomatic therapy to long term management. Lifestyle modification is usually the first line of treatment in most women. However, only a few studies have been conducted on effect of exercise on PCOS and none in Asian ethnic group. Following an
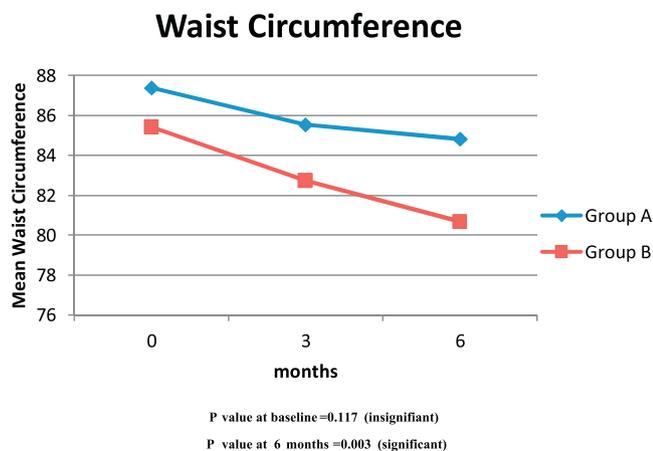
Waist Circumference

P value at baseline =0.117 (insignifiant)

P value at 6 months =0.003 (significant)

Fig. 3. Change in mean waist circumference in two groups.

exercise regime on a long term basis is a challenge for most. Therefore we kept an exercise regime which could be easily incorporated in one's daily schedule for better compliance and exercise was supervised in the initial phase. The objective measurement of intensity was also kept very simple for easy self monitoring by a large segment of women.

We found in our study that exercise led to significant improvement in women with oligomenorrhoea, polymenorrhoea and secondary amenorrhoea and metformin showed an additive influence. At 3 months 31% and 37.5% women improved in group A and B respectively and the corresponding figures at 6 months were 55% and 83%. In a study done by Palomba et al. [8], significant improvement in menstrual cycles and fertility was seen after 24 weeks of structured exercise and diet control, with no differences between the two groups. The frequency of menses and the ovulation rate were significantly higher in the exercise group but the increased cumulative pregnancy rate was not significant. A systematic review and meta-analysis of 12 RCTs comprising 608 women done by Naderpoor et al. [9] reported that lifestyle modification plus metformin is associated with improved menstruation at 6 months in women with PCOS compared with lifestyle modification with placebo.

In our study the mean difference in mFG score at 3 months and 6 months were significant within the groups but the significance was lost on comparing two groups. The mean difference in the exercise plus metformin group is almost three times that in exercise group alone. In a systematic review and meta-analysis [10] of RCTs of exercise alone or with lifestyle intervention in people with PCOS, it was found that mFG score improved significantly in women in lifestyle intervention vs usual care group with a mean difference of −1.0. Total testosterone levels were also improved significantly in lifestyle intervention group. Tang et al. [11] noted a significant reduction in the FAI and hirsutism score in the metformin arm of the study and a significant fall in total and free testosterone. However, the study was conducted only in obese women and duration of exercise was only 15 min daily for three months, which was not assessed formally.

It is also noted that exercise without weight loss or with only a moderate weight loss can still lead to a significant reduction in visceral fat and an improvement in insulin sensitivity [2–4]. In our study we noticed significant reductions in body weight leading to significantly improved body mass index, waist circumference and waist hip ratio within both the groups. Group B lost twice as much weight as compared to group A after 3 and 6 months of intervention. Group B showed significantly better Waist Circumference and Waist Hip Ratio but not the BMI. Palomba et al. [8] reported that body weight, body mass index, waist circumference,

changed significantly from in exercise only group and were significantly different between the exercise and diet group.

We found improvement in all women with deranged OGTT after 6 months. However, number of women with deranged OGTT was small and it's an indirect measure of insulin resistance. HOMA-IR scores are better indicator but due to logistical reason we were unable to measure it. Addition of metformin to exercise did not result in improvement in serum triglyceride and cholesterol in our study. In the study of Palomba et al. [8] insulin resistance indices changed. Ladson et al. [12] found that insulinogenic indices were unaltered in metformin group, with no significant change in triglyceride and cholesterol levels.

Side effects of metformin have not been a limiting factor in our study possibly because of motivation and gradual increase in dose. Short term compliance was excellent in our study however long term intake may become an issue especially if desired results are not observed.

There were limitations in our study as our study population was small, so they may not be the representative of whole population. Exercise of 30 min, 3 times a week was taken arbitrarily based on literature which was not standardized. However we found that simple exercise like marching was effective. Long term benefits of exercise will depend on compliance with regime and hence result cannot be extrapolated on general population. We found a very low dropout rate in our study. We recommend large multicentre studies for optimum duration of exercise in its simplest form. Also studies using more direct measure of insulin resistance (HOMA-IR) can provide more accurate information unlike OGTT, which is an indirect indicator.

Literature [13,14,15] suggests that exercise has beneficial effects in insulin resistant populations, independent of weight loss and our study confirms this. In our study we found that metformin adds to benefits on regularisation of menstrual cycle, weight, body mass index, waist circumference, waist hip ratio and hyperandrgenism and OGTT. However its effectiveness in improving hyperandrogenism, insulin resistance (HOMA-IR) and lipid profile needs studies with larger number of women with these abnormalities. Thus we conclude that regular exercise should be the first and foremost treatment for the women with PCOS. Metformin can be added to potentiate its benefits especially in women with oligomenorrhoea, polymenorrhoea and secondary amenorrhoea and may be those with clinical hirsuitism.

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