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Original Research Article

Comparison between the effects of low-dose spironolactone plus metformin and metformin alone on hormonal and biochemical parameters of insulin resistance in women with polycystic ovary syndrome

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a common endocrine disorder in reproductive-age women, characterized by insulin resistance and hyperandrogenism. Metformin improves insulin sensitivity, while spironolactone has antiandrogenic effects. Evidence regarding the short-term benefit of combining low-dose spironolactone with metformin remains inconclusive, particularly in South Asian populations. This study aimed to compare the effects of low-dose spironolactone plus metformin versus metformin alone on hormonal and biochemical parameters of insulin resistance in women with PCOS.

Methods: This randomized controlled trial was conducted at Bangabandhu Sheikh Mujib Medical University, Dhaka, from July 2023 to June 2024. Ninety women aged 18-40 years with PCOS (Rotterdam criteria), BMI 18-30 kg/m^2, and HOMA-IR>2 were randomized to receive either spironolactone (50 mg/day) plus metformin (1500 mg/day) or metformin alone (1500 mg/day) for 12 weeks. Hormonal and metabolic parameters were measured at baseline and post-treatment.

Results: Both groups showed significant improvements in BMI, waist circumference, serum LH, FSH, LH/FSH ratio, free testosterone, fasting glucose, fasting insulin, and HOMA-IR ($p<0.05$). The combination group demonstrated numerically greater reductions in LH (3.02 versus 1.92 µIU/ml), free testosterone (0.33 versus 0.22 pg/ml), and HOMA-IR (1.37 versus 1.11); however, none of the between-group differences were statistically significant ($p>0.05$).

Conclusions: Both low-dose spironolactone plus metformin and metformin alone significantly improve hormonal and insulin resistance parameters in women with PCOS. However, the addition of spironolactone does not provide a significant short-term advantage over metformin alone.

Keywords: Fetal distress, Hypertension in pregnancy, Stillbirths

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinological disorder affecting women of reproductive age.[1] It is characterized by menstrual irregularities, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound.[2] Insulin resistance (IR) with compensatory hyperinsulinemia is a key pathogenic feature of PCOS and plays a central role in its metabolic and reproductive manifestations. It contributes to hyperandrogenism by enhancing ovarian theca cell androgen production, potentiating luteinizing

hormone (LH) activity, and suppressing hepatic synthesis of sex hormone-binding globulin (SHBG), thereby increasing circulating free testosterone levels.[3,4]

Among the pharmacological options used in PCOS- including oral contraceptives, insulin sensitizers, antiandrogens, and ovulation induction agents- metformin, an oral biguanide, is the most widely studied insulin sensitizer. It improves peripheral insulin sensitivity, reduces hepatic gluconeogenesis, and has a direct inhibitory effect on ovarian theca cell androgen production.[5,6] However, metformin alone has shown inconsistent evidence in improving reproductive outcomes such as live birth rates among women with infertility associated with PCOS.[7]

Spironolactone, an aldosterone antagonist with antiandrogenic properties, reduces hyperandrogenic symptoms by blocking androgen receptors and inhibiting both ovarian and adrenal androgen synthesis. It is commonly used in the management of hirsutism and acne in PCOS.[8] Considering that insulin resistance and hyperandrogenism are closely interrelated pathogenic mechanisms in PCOS, combined therapy with metformin and low-dose spironolactone may provide additive or synergistic benefits.

Recent meta-analyses and randomized studies have reported that the combination of metformin and spironolactone leads to greater improvements in hormonal and metabolic parameters, including serum testosterone levels, insulin resistance indices, and fasting glucose, compared with metformin alone, particularly in studies with longer treatment durations.[9,10] Nevertheless, evidence remains limited regarding the effectiveness of low-dose spironolactone (50 mg/day) as an adjunct to metformin over a shorter treatment period, particularly in South Asian populations.

Therefore, this study aimed to compare the effects of low-dose spironolactone plus metformin versus metformin alone on hormonal parameters (serum LH, FSH, LH/FSH ratio, and free testosterone) and biochemical parameters of insulin resistance (fasting glucose, fasting insulin, and HOMA-IR) in women with PCOS.

METHODS

This randomized controlled trial was conducted at the department of reproductive endocrinology and infertility at Bangabandhu Sheikh Mujib Medical University (BSMMU) in Dhaka from July 2023 to June 2024. It involved 90 women aged 18-40 years with polycystic ovary syndrome (PCOS) and insulin resistance, diagnosed by Rotterdam criteria, with BMI between 18-30 kg/m^2 and HOMA-IR>2. Participants provided written consent and were excluded if they had endocrine disorders (like hypothyroidism, hyperthyroidism, hyperprolactinemia, or diabetes), other medical issues (renal, hepatic, cardiovascular diseases), recent use of drugs affecting insulin resistance (such as metformin or oral contraceptives), or contraindications to spironolactone or metformin. Using computer- generated permuted block randomization and allocation concealment via serially numbered opaque envelopes, women were randomly assigned in a 1:1 ratio to two groups: the experimental group (n=45), which received low-dose spironolactone (50 mg/day) plus metformin (1500 mg/day in divided doses), and the control group (n=45), which received only metformin (1500 mg/day) for 12 weeks. Fasting blood samples were collected at baseline and after treatment, following an overnight fast of at least 10 hours. Hormonal markers- serum LH, FSH, and free testosterone- were measured on day 2 of the menstrual cycle using electrochemiluminescence immunoassay (Roche Diagnostics) at the department of biochemistry, BSMMU. Biochemical parameters such as fasting glucose, fasting insulin, and HOMA-IR were also assessed. During the study, patients were contacted monthly by phone to monitor compliance and record adverse effects. After 12 weeks, 43 patients from the spironolactone plus metformin group and 42 from the metformin- only group completed the study, with dropout rates of 4.4% and 6.7% respectively. Data analysis was performed using SPSS version 23.0. Continuous variables were expressed as mean±standard deviation; categorical data as frequencies and percentages. Paired t-tests compared pre- and post-treatment results within groups, while independent t-tests or Mann-Whitney U tests compared differences between groups, depending on data distribution. The chi-square test assessed categorical variables. A p value less than 0. 0.05 was considered statistically significant. Ethical approval was obtained from the BSMMU institutional review board, and the study adhered to the Declaration of Helsinki. All participants gave written informed consent, and privacy, anonymity, and confidentiality were maintained throughout.

RESULTS

Ninety women with PCOS and insulin resistance participated in this trial, with 45 in each group. After 12 weeks, 43 (95.6%) in the spironolactone plus metformin group and 42 (93.3%) in the metformin group completed the study. Dropout rates were 4.4% and 6.7%, mainly due to personal reasons. Demographic characteristics, including age, occupation, residence, infertility type, BMI, waist circumference, and clinical presentations, showed no significant differences (p>0.05).

Table 1 shows that mean age was 25.2±3.5 years in spironolactone +metformin group and 25.4±3.9 years in metformin alone group. Majority of the patients were housewives in both the groups. Maximum came from urban region. Most of the patients in both the groups had primary infertility. There was no significant difference regarding age, occupational status, residence and type of infertility between two groups.

Table 1: Demographic characteristics of study population (n=90).

Demographic characteristics		Spironolactone + Metformin (n=45)		Metformin alone (n=45)		P value
		N	%	N	%	
Age (years)	18-21	6	13.33	6	13.33	0.798^{ns}
	22-25	18	40	20	44.44	
	26-29	16	35.56	11	24.44	
	30-35	5	11.11	8	17.78	
	Mean±SD	25.2±3.5		25.4±3.9		
	Range (min-max)	19-35		19 -34		
Occupational status	House wife	38	84.44	36	80	0.571^{ns}
	Service	7	15.56	8	17.78	
	Student	0	0	1	2.22	
Residence	Rural	16	35.56	13	28.89	0.499^{ns}
	Urban	29	64.44	32	71.11	
Infertility	Primary	38	84.44	35	77.78	0.419^{ns}
	Secondary	7	15.56	10	22.22	

*Numerical variables are describing as mean±standard deviation or categorical variables as frequency (%). ns= not significant; P values was calculated using Student's t-test and Chi-square test.

Table 2: Clinical presentations of the study participants (n=90).

Parameters	Spironolactone+ Metformin (n=45)		Metformin alone (n=45)		P value
	N	%	N	%	
Oligomenorrhea	44	97.78	43	95.56	0.500^{ns}
Hirsutism	40	88.89	41	91.11	0.500^{ns}
Acne	23	51.11	18	40	0.290^{ns}
Acanthosis nigricans	34	75.56	32	71.11	0.634^{ns}

*Categorical variables as frequency (%). ns= not significant; P-values was calculated using Chi-square test.

Table 3: Pre and post-treatment clinical, hormonal, and insulin resistance parameters in the spironolactone + metformin group.

Variables	Pre-treatment (n=43*) Mean±SD	Post treatment (n=43*) Mean±SD	Mean difference (95% confidence interval)	P value
BMI (kg/m^2)	26±2.4	24.9±2.2	0.98 (0.85 to 1.12)	0.001^{s}
Waist circumference (cm)	89.8±6.1	88.7±5.8	0.90 (0.65 to 1.15)	0.001^{s}
Serum LH (µIU/ml)	9.5±3.1	7.4±3.8	2.16 (0.90 to 3.41)	0.001^{s}
Serum FSH (µIU/ml)	5.4±1.2	5.1±1.0	0.31 (0.15-0.47)	0.001^{s}
Serum LH/FSH ratio	1.82±0.67	1.51±0.96	0.31 (0.01 to 0.61)	0.043^{ns}
Serum free testosterone (pg/ml)	2.95±2.20	2.39±2.39	0.63 (0.14 to 1.12)	0.012^{ns}
Fasting glucose (mmol/l)	5.2±0.4	4.8±0.4	0.32 (0.19 to 0.45)	0.001^{s}
Fasting insulin (µIU/ml)	14.9±3.8	9.7±2.7	5.31 (4.13 to 6.48)	0.001^{s}
HOMA-IR	3.43±0.97	2.07±0.61	1.37 (1.07 to 1.67)	0.001^{s}

*2 patients dropped out in follow up period. Numerical variables are described as mean ± standard deviation. s= significant; ns= not significant; p value was calculated using a paired t- test.

Table 2 shows that oligomenorrhea was found in 44 (97.78%) in spironolactone+ metformin group and 43 (95.56%) in metformin alone group. 40 (88.89%) patients had hirsutism in spironolactone+ metformin group against 41 (91.11%) participants with hirsutism in metformin alone group. Acne was present in 23 (51.11%) patients in the spironolactone+ metformin group and 18 (40.0%) patients in the metformin alone group. 34 (75.56%) and 32 (71.1%) patients presented with acanthosis nigricans in the spironolactone + metformin and metformin alone groups, respectively. The differences between the two arms were not statistically significant.

Table 3 shows significant improvements in clinical, hormonal, and insulin resistance parameters among 43 women with PCOS after 12 weeks of low-dose spironolactone plus metformin. BMI decreased from 26.0±2.4 to 24.9±2.2 kg/m^2, waist circumference from

89.8±6.1 to 88.7±5.8 cm, serum LH from 9.5±3.1 to 7.4±3.8 µIU/ml, FSH from 5.4±1.2 to 5.1±1.0, LH/FSH ratio from 1.82±0.67 to 1.51±0.96, serum free testosterone from 2.95±2.20 to 2.39±2.39 pg/ml, fasting glucose from 5.2±0.4 to 4.8±0.4 mmol/l, fasting insulin from 14.9±3.8 to 9.7±2.7 µIU/ml, and HOMA-IR from 3.43±0.97 to 2.07±0.61. All changes were statistically significant, indicating the combination therapy effectively improves parameters in women with PCOS after 12 weeks.

Table 4: Pre and post-treatment clinical, hormonal, and insulin resistance parameters in the metformin alone group.

Variables	Pre-treatment (n=45) Mean±SD	Post-treatment (n=42*) Mean±SD	Mean difference (95% confidence interval)	P value
BMI (kg/m^2)	26.2±2.6	25.5±2.7	0.91 (0.79 to 1.04)	0.001^s
Waist circumference (cm)	90.2±6.2	89.5±6.3	0.88 (0.64 to 1.12)	0.001^s
Serum LH (µIU/ml)	8.8±2.8	7±2.7	1.91 (1.31 to 2.50)	0.001^s
Serum FSH (µIU/ml)	5.6±1.5	5.2±1.5	0.33 (0.16 to 0.51)	0.001^s
Serum LH/FSH ratio	1.62±0.49	1.4±0.61	0.24 (0.11 to 0.37)	0.001^s
Serum free testosterone (pg/ml)	2.89±1.85	2.59 ±1.84	0.31 (0.11 to 0.50)	0.002^s
Fasting glucose (mmol/l)	5.1±0.4	4.9±0.5	0.24 (0.15 to 0.34)	0.001^s
Fasting insulin (µIU/ml)	15.5±4.6	10.8±2.8	4.51 (3.20 to 5.82)	0.001^s
HOMA-IR	3.48±0.95	2.34±0.64	1.11 (0.83 to 1.40)	0.001^s

*3 patients dropped out in follow up period. Numerical variables are described as mean ± standard deviation. s= significant; p value was calculated using a paired t-test.

Table 5: Outcomes of clinical, hormonal, and insulin resistance parameters between the two groups.

Parameters	Spironolactone + metformin (n=43)	Metformin alone (n=42)	P value
Clinical Parameters (Mean Change±SD)			
Δ BMI (kg/m^2)	0.98±0.44	0.91±0.39	0.436^{*ns}
Δ Waist Circumference (cm)	0.90±0.81	0.88±0.77	0.88^{*ns}
Hormonal Parameters (Median Change, IQR)			
Δ Serum LH (µIU/ml)	3.02 (1.20-4.47)	1.92 (1.10-3.20)	0.076^{**ns}
Δ Serum FSH (µIU/ml)	0.26 (0.03-0.72)	0.22 (0.04-0.53)	0.909^{**ns}
Δ LH/FSH Ratio	0.42 (0.10-0.75)	0.25 (0.01-0.55)	0.089^{**ns}
Δ Free Testosterone (pg/ml)	0.33 (0.15-1.09)	0.22 (0.09-0.50)	0.162^{**ns}
Insulin Resistance Parameters (Mean Change±SD)			
Δ Fasting glucose (mmol/l)	0.32±0.42	0.24±0.30	0.362^{*ns}
Δ Fasting insulin (µIU/ml)	5.31±3.80	4.51±4.20	0.366^{*ns}
Δ HOMA-IR	1.37±0.97	1.11±0.90	0.212^{*ns}

Numerical variables are described as mean ± standard deviation. ns= not significant; *p value was calculated using Student's t- test; **p value was calculated using the Mann-Whitney U test.

Table 6: Side effects of the study population.

Variables	Spironolactone + Metformin (n=43)		Metformin alone (n=42)		P value
	N	%	N	%	
Nausea	4	9.30	5	11.9	0.485^{ns}
Vomiting	1	2.33	1	2.38	0.747^{ns}
Diarrhea	3	6.98	1	2.38	0.317^{ns}

*Categorical variables as frequency (%). Ns= not significant; p values was calculated using Chi-square test.

Table 4 demonstrates that, within the group treated solely with metformin, the mean BMI and waist circumference showed a statistically significant reduction from pre-treatment values following a 3-month intervention. Regarding hormonal parameters, the mean serum LH, FSH, LH/FSH ratio, and free testosterone levels significantly declined from pre-treatment levels after 3 months of intervention. Regarding insulin resistance indicators, mean fasting glucose, fasting insulin, and HOMA-IR likewise showed significant decreases from baseline after the three-month treatment period.

Table 5 compares outcomes between 43 women with PCOS receiving low-dose spironolactone plus metformin

and 42 women taking only metformin over 12 weeks. It presents median changes (interquartile range) for hormonal parameters and mean changes (±SD) for insulin resistance and clinical metrics. No significant differences were observed: BMI reduction was 0.98 kg/m^2 versus 0.91 (p=0.436), waist circumference 0.90 cm versus 0.88 (p=0.880). The combination group showed greater median hormonal decreases: serum LH 3.02 µIU/ml versus 1.92 µIU/ml (p=0.076), FSH 0.26 versus 0.22 µIU/ml (p=0.909), LH/FSH ratio 0.42 versus 0.25 (p=0.089), free testosterone 0.33 versus 0.22 pg/ml (p=0.162). Although these differences appeared better numerically, they were not statistically significant. Insulin resistance parameters also favoured the combination: fasting glucose decreased by 0.32 mmol/l versus 0.24 mmol/l (p=0.362), fasting insulin decreased by 5.31 µIU/ml versus 4.51 µIU/ml (p=0.366), and HOMA-IR decreased by 1.37 versus 1.11 (p=0.212).

Table 6 indicates that the incidence of side effects was comparatively higher in the group receiving spironolactone combined with metformin than in the group receiving metformin alone. The differences observed were not statistically significant (p>0.05). Overall, both medications were well tolerated, with only a few side effects reported.

DISCUSSION

This randomized controlled trial compared low-dose spironolactone plus metformin versus metformin alone in 90 women with PCOS over 12 weeks. Both treatment regimens produced significant improvements in clinical, hormonal, and insulin resistance parameters from baseline. However, no statistically significant differences were observed between the groups (p>0.05). These findings suggest that while both therapies are effective in the short term, the additional benefit of low-dose spironolactone may not be fully apparent within a 12-week treatment period.

Baseline demographic and clinical characteristics were comparable between the two groups, indicating successful randomization and minimizing the likelihood of confounding. The mean age was 25.2±3.5 years in the combination group and 25.4±3.9 years in the metformin group, which is similar to findings from a recent Bangladeshi study reporting a mean age of 25.1 years.[11] The predominance of younger women in this study likely reflects earlier healthcare-seeking behaviour due to menstrual irregularities, infertility concerns, and sociocultural factors. Oligomenorrhea was the most common clinical presentation, followed by hirsutism, acne, and acanthosis nigricans, mirroring the clinical profile reported in previous Bangladeshi studies.[11]

In the spironolactone plus metformin group, significant improvements were observed across several metabolic and hormonal parameters after 12 weeks of treatment. BMI decreased from 26.0±2.4 to 24.9±2.2 kg/m^2 (p=0.001), LH from 9.5±3.1 to 7.4±3.8 µIU/ml (p=0.001), free testosterone from 2.95±2.20 to 2.39±2.39 pg/ml (p=0.012), and HOMA-IR from 3.43±0.97 to 2.07±0.61 (p=0.001). These findings indicate favorable effects on both hyperandrogenism and insulin resistance. Similar benefits have been reported in a 2025 meta-analysis demonstrating significant improvements in hormonal and metabolic outcomes with combination therapy.[12] Notably, the reduction of HOMA-IR to below 2.5 suggests a clinically meaningful improvement in insulin sensitivity.

Likewise, the metformin-only group demonstrated significant within-group improvements in all assessed parameters. BMI decreased from 26.2±2.6 to 25.5±2.7 kg/m² (p=0.001), LH from 8.8±2.8 to 7.0±2.7 µIU/ml (p=0.001), and HOMA-IR from 3.48±0.95 to 2.34±0.64 (p=0.001). These results reaffirm the established role of metformin in improving metabolic dysfunction and insulin resistance in women with PCOS. Recent evidence suggests that metformin enhances insulin clearance and metabolic regulation, partly through weight reduction.[13] Given its affordability, availability, and favorable safety profile, metformin remains a practical first-line therapeutic option, particularly in resource-constrained settings.

The principal finding of the present study was the absence of statistically significant differences between the treatment groups despite consistently greater numerical improvements in the combination therapy arm. Although the reduction in LH was greater with spironolactone plus metformin (3.02 versus 1.92 µIU/mL), the difference did not reach statistical significance (p=0.076). This trend may indicate a potential additive effect of spironolactone that was underpowered to achieve significance. The relatively small sample size, short duration of follow-up, and use of a low spironolactone dose (50 mg/day) may have limited the ability to detect clinically relevant between-group differences. It is possible that longer treatment duration or higher doses could produce more pronounced benefits.

The present findings are consistent with recent systematic reviews and meta-analyses that reported no significant superiority of spironolactone plus metformin over metformin alone in improving BMI, androgen levels, or manifestations of clinical hyperandrogenism.[14,15] Nevertheless, considerable heterogeneity among studies and the limited number of high-quality randomized trials remain important limitations in the existing evidence base. These observations suggest that treatment outcomes may vary according to individual PCOS phenotypes, and women with more severe hyperandrogenic features may derive greater benefit from adjunctive spironolactone therapy.

Both treatment regimens were well tolerated throughout the study period. Only mild gastrointestinal adverse effects were reported, with a slightly higher frequency of diarrhoea in the combination group (6.98% versus 2.38%), although this difference was not statistically significant. Importantly, no participant discontinued treatment because

of adverse events, indicating good treatment adherence and overall tolerability of both regimens.

Ongoing studies such as the SPIOMET4HEALTH trial may provide further insights into the role of spironolactone-containing combination therapies in PCOS management.[16,17] This large multicenter randomized trial is expected to generate stronger evidence regarding long-term hormonal, metabolic, and reproductive outcomes and may help identify patient subgroups most likely to benefit from combination treatment strategies.

This study contributes valuable randomized evidence from a South Asian population, where data on combination therapy for PCOS remain limited. The high follow-up completion rates (95.6% and 93.3%) and robust randomization process enhance the reliability and internal validity of the findings. From a clinical perspective, the results support the continued use of metformin as an effective first-line treatment for PCOS while suggesting that the addition of spironolactone may be considered in selected patients, particularly those with persistent hyperandrogenic symptoms or inadequate response to metformin alone.

This study has several limitations. The sample size was relatively small, and the treatment duration was only 12 weeks. A six-month follow-up would have provided more definitive answers, and this serves as an important lesson for future study design. Participants and investigators were not blinded. In hindsight, a double-blind design would have strengthened the validity of our findings. The study was conducted at a single tertiary care centre in Bangladesh, limiting the generalizability of the results. Our patient population may represent a more severe spectrum of PCOS. Furthermore, lifestyle factors were not standardised; during the study, significant variability in participants' lifestyle practices likely influenced the outcomes.

CONCLUSION

Low-dose spironolactone combined with metformin and metformin alone both significantly improved serum LH, FSH, LH/FSH ratio, free testosterone, fasting glucose, fasting insulin, and HOMA-IR in women with polycystic ovary syndrome. However, no statistically significant differences were observed in post-treatment hormonal and biochemical parameters between the two groups.

These findings suggest that while both treatment regimens are effective in improving metabolic and hormonal abnormalities in PCOS, the addition of low-dose spironolactone does not provide a significant short-term advantage over metformin alone.

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