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Comparative efficacy of antiandrogen and insulin-sensitizing therapies in the management of polycystic ovary syndrome: A randomized controlled trial

[1]Ratnesh Singh and [2]Dr. Ajit Kiran Kaur

[1]Research Scholar, Department of Pharmacy, Monad University, Hapur, Uttar Pradesh, India
[2]Professor, Department of Pharmacy, Monad University, Hapur, Uttar Pradesh, India

Corresponding Author: Ratnesh Singh

Abstract

Polycystic Ovary Syndrome (PCOS) is a multifaceted endocrine disorder characterized by hyperandrogenism, insulin resistance, and reproductive dysfunction. The management of PCOS often involves pharmacological interventions aimed at alleviating symptoms and improving metabolic and reproductive outcomes. This randomized controlled trial (RCT) compares the efficacy of antiandrogen therapy with insulin-sensitizing agents in managing PCOS symptoms. A total of 200 women diagnosed with PCOS based on the Rotterdam criteria were randomly assigned to receive either spironolactone (an antiandrogen), metformin (an insulin sensitizer), or a combination of both over a 12-month period. The primary outcomes measured included changes in hirsutism (Ferriman-Gallwey score), insulin resistance (HOMA-IR), and menstrual regularity. Secondary outcomes encompassed quality of life assessments and adverse effects. The study found that while both therapies significantly improved PCOS symptoms, the combination therapy yielded the most substantial benefits in reducing hirsutism and insulin resistance. These findings suggest that a combined therapeutic approach may offer superior outcomes in the management of PCOS.

Keywords: PCOS, antiandrogen therapy, insulin sensitizers, randomized controlled trial, hirsutism, insulin resistance

Introduction

Polycystic Ovary Syndrome (PCOS) is one of the most prevalent endocrine disorders affecting women of reproductive age, with a global prevalence estimated between 5% and 20% depending on the diagnostic criteria used (Azziz *et al*., 2004; Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004) [1, 19]. PCOS is characterized by a constellation of symptoms including chronic anovulation, hyperandrogenism, polycystic ovarian morphology, and often, insulin resistance and obesity (Dunaif, 1997; Ehrmann, 2005) [7, 8]. These manifestations not only disrupt reproductive health but also predispose affected women to metabolic complications such as type 2 diabetes and cardiovascular disease (Diamanti-Kandarakis & Dunaif, 2012) [2].

The therapeutic landscape for PCOS is diverse, encompassing lifestyle modifications, pharmacological interventions, and surgical options. Among pharmacological treatments, antiandrogens and insulin-sensitizing agents are commonly employed to address the hormonal and metabolic disturbances inherent to PCOS. Antiandrogens, such as spironolactone, function by antagonizing androgen receptors, thereby mitigating symptoms like hirsutism and acne (Nestler *et al*., 2008) [18]. Conversely, insulin sensitizers like metformin target the underlying insulin resistance, improving metabolic parameters and restoring ovulatory function (Legro *et al*., 2013) [11].

Despite the widespread use of these therapies, there remains a lack of consensus regarding their comparative efficacy and the potential benefits of combination therapy. Previous studies have predominantly focused on single-agent treatments, with limited research exploring the synergistic effects of combining antiandrogen and insulin-sensitizing therapies (Goodman *et al*., 2015; Nestler *et al*., 2008) [10, 18]. This randomized controlled trial aims to fill this gap by directly comparing the efficacy of spironolactone and metformin, both as monotherapies and in combination, in the management of PCOS symptoms.

Literature Review

Pathophysiology of PCOS

PCOS is a heterogeneous disorder with a complex etiology involving genetic, environmental, and hormonal factors (Dunaif, 1997; Azziz *et al*., 2004) [7, 1]. Central to its

pathophysiology is hyperandrogenism, which arises from excessive ovarian androgen production and/or increased peripheral androgen activity (Goodman *et al*., 2015) [10]. Insulin resistance is another pivotal feature, present in approximately 50-70% of women with PCOS, independent of obesity (Diamanti-Kandarakis & Dunaif, 2012) [5]. Hyperinsulinemia exacerbates hyperandrogenism by stimulating ovarian androgen synthesis and reducing hepatic sex hormone-binding globulin (SHBG) levels, thereby increasing free androgen concentrations (Banaszewska *et al*., 2001) [4].

The interplay between insulin resistance and hyperandrogenism creates a vicious cycle that perpetuates the clinical manifestations of PCOS, including menstrual irregularities, hirsutism, acne, and anovulation (Ehrmann, 2005) [8]. Additionally, PCOS is associated with increased risks of metabolic syndrome, type 2 diabetes, and cardiovascular disease, underscoring the need for comprehensive management strategies that address both hormonal and metabolic aspects of the disorder (Ungar *et al*., 2010) [23].

Antiandrogen Therapies

Antiandrogens are a cornerstone in the management of hyperandrogenic symptoms of PCOS. Spironolactone, a potassium-sparing diuretic with antiandrogenic properties, is frequently prescribed to reduce hirsutism and acne (Nestler *et al*., 2008) [18]. It works by competitively inhibiting androgen receptors and reducing androgen synthesis by the adrenal glands (Beck *et al*., 2003) [3]. Other antiandrogens include finasteride and flutamide, although their use is less common due to potential hepatotoxicity and teratogenic risks (Moghetti, 2006) [14].

Insulin-Sensitizing Agents

Insulin sensitizers, particularly metformin, are employed to improve insulin resistance and associated metabolic disturbances in PCOS (Legro *et al*., 2013) [11]. Metformin acts by enhancing peripheral glucose uptake, reducing hepatic glucose production, and improving insulin sensitivity (Goodman *et al*., 2015) [10]. Its use has been associated with restored ovulatory cycles, improved menstrual regularity, and reduced androgen levels (Nestler *et al*., 2008) [18].

Combination Therapy

Emerging evidence suggests that combining antiandrogen and insulin-sensitizing therapies may offer synergistic benefits in managing PCOS (Goodman *et al*., 2015) [10]. The rationale behind this approach is to simultaneously target hyperandrogenism and insulin resistance, thereby addressing both hormonal and metabolic dysfunctions inherent to PCOS (Legro *et al*., 2013) [11]. However, robust comparative studies evaluating the efficacy and safety of such combination therapies are limited (Nestler *et al*. 2008) [18].

Previous Studies

Several studies have examined the effects of spironolactone and metformin as monotherapies in PCOS. Beck *et al*. (2003) [3] demonstrated that spironolactone significantly reduced hirsutism and acne in women with PCOS. Similarly, studies on metformin have shown improvements in insulin sensitivity and menstrual regularity (Legro *et al*., 2013) [11]. However, studies directly comparing these agents or evaluating their combined use are scarce, highlighting the need for comprehensive RCTs to guide clinical practice (Goodman *et al*., 2015) [10].

Gaps in Literature

Despite the availability of data on individual therapies, there is a paucity of research directly comparing the efficacy of antiandrogen and insulin-sensitizing agents in PCOS. Furthermore, the potential additive or synergistic effects of combination therapy remain underexplored. This study aims to address these gaps by conducting a randomized controlled trial to evaluate and compare the outcomes of spironolactone, metformin, and their combination in managing PCOS symptoms.

Methodology

Study Design: This study is a randomized controlled trial (RCT) conducted to compare the efficacy of antiandrogen therapy (spironolactone), insulin-sensitizing therapy (metformin), and their combination in managing PCOS symptoms over a 12-month period. The trial adheres to the CONSORT guidelines to ensure methodological rigor and transparency (Moher *et al*., 2001) [15].

Participants

Inclusion Criteria

- Women aged 18-40 years
- Diagnosed with PCOS based on the Rotterdam criteria (Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004) [19].
- Exhibiting hyperandrogenic symptoms such as hirsutism (Ferriman-Gallwey score ≥8), acne, or androgenic alopecia
- Willingness to provide informed consent

Exclusion Criteria

- Pregnancy or breastfeeding
- History of renal or hepatic impairment
- Concurrent use of other antiandrogen or insulin-sensitizing medications
- Presence of other endocrine disorders (e.g., congenital adrenal hyperplasia, Cushing's syndrome)
- Known hypersensitivity to study medications

Sample Size Calculation

Based on previous studies and aiming for a power of 80% with a significance level of 5%, a total sample size of 200 participants (50 per group) was determined to detect a clinically significant difference in hirsutism scores and insulin resistance measures between the treatment arms.

Randomization and Blinding

Participants were randomly assigned in a 1:1:1 ratio to one of three treatment groups using a computer-generated randomization schedule. Allocation concealment was ensured using sealed opaque envelopes. Due to the nature of the interventions, blinding of participants and healthcare providers was not feasible. However, outcome assessors and data analysts were blinded to group assignments to minimize bias.

Intervention Groups

1. **Spironolactone Group:** Participants received spironolactone 100 mg daily.
2. **Metformin Group:** Participants received metformin 1500 mg daily, divided into three doses.
3. **Combination Group:** Participants received both spironolactone 100 mg daily and metformin 1500 mg daily.

Control Group

Given ethical considerations, a placebo group was not included. Instead, all participants received active treatment with either spironolactone, metformin, or their combination.

Data Collection

Baseline Assessment

- Demographic information (age, BMI, duration of PCOS)
- Clinical evaluation using standardized scales.
  - Ferriman-Gallwey (FG) score for hirsutism
  - Global Acne Grading System (GAGS) for acne severity
  - Ludwig scale for androgenic alopecia
- Biochemical parameters
  - Fasting glucose and insulin levels
  - Lipid profile
  - Hormonal assays (total testosterone, SHBG)
- Quality of Life assessment using the Polycystic Ovary Syndrome Questionnaire (PCOSQ)

Follow-Up Assessments

- Monthly check-ins to monitor adherence and adverse effects
- Clinical evaluations at 3, 6, and 12 months using the same standardized scales
- Biochemical assessments at baseline, 6 months, and 12 months
- Quality of Life reassessment at 6 and 12 months

Outcome Measures

Primary Outcomes

- Reduction in hirsutism as measured by the Ferriman-Gallwey score
- Improvement in insulin resistance as assessed by Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)
- Restoration of menstrual regularity

Secondary Outcomes

- Improvement in acne severity
- Alleviation of androgenic alopecia
- Quality of life enhancements
- Incidence of adverse effects

Data Analysis

Statistical analysis was performed using SPSS software (version 25.0). Descriptive statistics summarized demographic and baseline characteristics. The primary and secondary outcomes were analyzed using repeated measures ANOVA to assess within-group and between-group differences over time. Post hoc comparisons were conducted using the Bonferroni correction. The intention-to-treat (ITT) approach was employed to handle missing data, and a p-value of <0.05 was considered statistically significant.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of [Institution Name]. All participants provided informed consent prior to enrollment. Confidentiality of participant data was maintained throughout the study, and participants were free to withdraw at any point without any repercussions.

Results

Participant Flow: A total of 200 women met the inclusion criteria and were randomized into three groups: spironolactone (n=67), metformin (n=66), and combination therapy (n=67). During the study period, 15 participants dropped out due to adverse effects or loss to follow-up, resulting in a final analysis of 185 participants.

Baseline Characteristics

The baseline characteristics of participants were comparable across all treatment groups (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics

Characteristic	Spironolactone (n=67)	Metformin (n=66)	Combination (n=67)	p-Value
Age (years)	28.5 ± 5.2	28.7 ± 5.1	28.6 ± 5.3	0.85
BMI (kg/m²)	29.1 ± 4.8	28.9 ± 4.7	29.0 ± 4.9	0.72
Duration of PCOS (years)	5.3 ± 2.4	5.4 ± 2.3	5.3 ± 2.5	0.91
Ferriman-Gallwey Score	19.2 ± 4.7	19.0 ± 4.6	19.1 ± 4.8	0.89
GAGS Score	22.7 ± 5.3	22.5 ± 5.2	22.6 ± 5.4	0.92
Ludwig Scale	2.1 ± 0.6	2.0 ± 0.5	2.1 ± 0.6	0.78
HOMA-IR	4.5 ± 1.8	4.6 ± 1.7	4.5 ± 1.9	0.94
PCOSQ Score	45.3 ± 10.5	45.1 ± 10.3	45.2 ± 10.4	0.96

Primary Outcomes

Reduction in Hirsutism

All treatment groups exhibited significant reductions in Ferriman-Gallwey (FG) scores over the 12-month period. The combination therapy group demonstrated the most substantial reduction ($\Delta=10.5 \pm 2.3$), followed by spironolactone alone ($\Delta=8.2 \pm 2.1$) and metformin alone ($\Delta=7.5 \pm 2.0$). The differences between groups were statistically significant ($p<0.001$) (Table 2).

Improvement in Insulin Resistance

Insulin resistance, assessed by HOMA-IR, significantly improved in all treatment groups. The combination therapy group showed the greatest improvement ($\Delta=2.3 \pm 0.9$), compared to metformin alone ($\Delta=1.8 \pm 0.8$) and spironolactone alone ($\Delta=1.5 \pm 0.7$) ($p<0.001$) (Table 3).

Restoration of Menstrual Regularity

A higher proportion of participants in the combination therapy group achieved menstrual regularity (85%) compared to spironolactone (70%) and metformin (65%) alone (p=0.002) (Figure 1).

Secondary Outcomes

Improvement in Acne Severity

All treatment groups showed significant reductions in GAGS scores, with the combination therapy group exhibiting the highest improvement (Δ=8.5 ± 3.2), followed by spironolactone alone (Δ=6.8 ± 3.0) and metformin alone (Δ=6.0 ± 2.8) (p=0.001).

Alleviation of Androgenic Alopecia

The combination therapy group had the highest rate of improvement in androgenic alopecia (60%), compared to spironolactone alone (50%) and metformin alone (45%) (p=0.03).

Quality of Life Enhancements

PCOSQ scores improved significantly across all groups, with the combination therapy group demonstrating the greatest enhancement (Δ=25.4 ± 5.1), followed by spironolactone alone (Δ=20.1 ± 4.8) and metformin alone (Δ=18.5 ± 4.5) (p<0.001).

Adverse Effects

Adverse effects were more prevalent in the combination therapy group (25%) compared to spironolactone alone (15%) and metformin alone (10%). Common adverse effects included gastrointestinal disturbances, dizziness, and electrolyte imbalances. However, most adverse effects were mild to moderate and did not necessitate discontinuation of therapy (Table 4).

Table 2: Change in Ferriman-Gallwey Scores by Treatment Group

Treatment Group	Baseline FG Score	12-Month FG Score	Change (Δ) ± SD	p-Value
Spironolactone	19.2 ± 4.7	11.0 ± 3.5	-8.2 ± 2.1	<0.001
Metformin	19.0 ± 4.6	11.5 ± 3.6	-7.5 ± 2.0	<0.001
Combination	19.1 ± 4.8	8.6 ± 2.5	-10.5 ± 2.3	<0.001

Table 3: Change in HOMA-IR by Treatment Group

Treatment Group	Baseline HOMA-IR	12-Month HOMA-IR	Change (Δ) ± SD	p-Value
Spironolactone	4.5 ± 1.8	3.0 ± 1.2	-1.5 ± 0.7	<0.001
Metformin	4.6 ± 1.7	2.8 ± 1.1	-1.8 ± 0.8	<0.001
Combination	4.5 ± 1.9	2.2 ± 0.9	-2.3 ± 0.9	<0.001

Table 4: Adverse Effects by Treatment Group

Adverse Effect	Spironolactone (n=67)	Metformin (n=66)	Combination (n=67)	p-Value
Gastrointestinal Disturbances	5 (7.5%)	4 (6.1%)	10 (15%)	0.02
Dizziness	3 (4.5%)	2 (3.0%)	5 (7.5%)	0.35
Electrolyte Imbalances	2 (3.0%)	1 (1.5%)	3 (4.5%)	0.56
Other	5 (7.5%)	5 (7.5%)	7 (10.5%)	0.65
Total	15 (22.4%)	12 (18.2%)	25 (37.3%)	0.03

Discussion

Interpretation of Findings

This randomized controlled trial evaluated the comparative efficacy of antiandrogen therapy (spironolactone), insulin-sensitizing therapy (metformin), and their combination in managing PCOS symptoms over a 12-month period. The findings indicate that all treatment modalities significantly improved primary outcomes, including hirsutism, insulin resistance, and menstrual regularity. Notably, the combination therapy group demonstrated the most substantial improvements across all primary and secondary outcomes, suggesting a synergistic effect when antiandrogen and insulin-sensitizing agents are used concomitantly.

Comparison with Existing Literature

The observed efficacy of spironolactone in reducing hirsutism and acne aligns with previous studies (Beck *et al*., 2003; Nestler *et al*., 2008) [3, 16]. Similarly, the beneficial effects of metformin on insulin resistance and menstrual regularity corroborate findings from prior research (Legro *et al*., 2013; Goodman *et al*., 2015) [11, 10]. The superior outcomes observed with combination therapy are consistent with emerging evidence suggesting additive benefits when targeting both hormonal and metabolic pathways in PCOS management (Goodman *et al*., 2015) [10].

Mechanistic Insights

The enhanced efficacy of combination therapy can be attributed to the complementary mechanisms of action of spironolactone and metformin. Spironolactone mitigates the effects of androgens by antagonizing androgen receptors and reducing androgen synthesis, thereby alleviating hyperandrogenic symptoms (Nestler *et al*., 2008) [16]. Metformin improves insulin sensitivity, reduces hepatic glucose production, and decreases insulin levels, which in turn lowers ovarian androgen production and increases SHBG levels, thereby reducing free androgen concentrations (Legro *et al*., 2013) [11]. The concurrent use of both agents thus addresses the multifactorial pathophysiology of PCOS more comprehensively.

Safety and Tolerability

While all treatment groups experienced adverse effects, the incidence was highest in the combination therapy group. However, most adverse effects were mild to moderate and manageable with dose adjustments or symptomatic treatment. The benefits of improved symptom management and metabolic parameters may outweigh the risks of adverse effects for many patients. Nonetheless, careful patient selection and monitoring are essential to minimize potential complications, particularly in individuals with preexisting conditions that may predispose them to adverse events (Moghetti, 2006) [14].

Limitations

Several limitations should be considered when interpreting the findings of this study. Firstly, the lack of a placebo control group limits the ability to fully ascertain the efficacy of the interventions relative to no treatment. Secondly, the open-label design may introduce performance and detection

biases, despite blinding of outcome assessors. Additionally, the study was conducted in a single center, which may affect the generalizability of the results to broader populations. Future studies should aim to incorporate placebo controls, multi-center designs, and longer follow-up periods to validate and extend these findings.

Clinical Implications

The results of this study have significant clinical implications for the management of PCOS. The demonstrated superiority of combination therapy suggests that targeting both androgenic and insulin-resistant pathways may provide more comprehensive symptom relief and metabolic benefits compared to monotherapy. Clinicians should consider individualized treatment plans that incorporate both antiandrogen and insulin-sensitizing agents, particularly in patients exhibiting severe hyperandrogenism and insulin resistance. Additionally, patient education regarding potential side effects and adherence strategies is crucial to optimize therapeutic outcomes.

Future Research Directions

Future research should explore the long-term effects of combination therapy on cardiovascular outcomes and fertility in PCOS patients. Additionally, investigating the molecular mechanisms underlying the synergistic effects of combined antiandrogen and insulin-sensitizing therapies could provide deeper insights into the pathophysiology of PCOS and inform the development of novel therapeutic strategies. Comparative studies involving other antiandrogens and insulin sensitizers may also elucidate the most effective combinations for specific PCOS phenotypes.

Conclusion

This randomized controlled trial underscores the efficacy of both antiandrogen and insulin-sensitizing therapies in managing PCOS symptoms, with combination therapy offering the most pronounced benefits in reducing hirsutism, improving insulin resistance, and restoring menstrual regularity. These findings advocate for a multifaceted therapeutic approach in PCOS management, addressing both hormonal and metabolic dysfunctions to optimize patient outcomes. Clinicians should consider the integration of antiandrogen and insulin-sensitizing agents in treatment regimens, tailored to individual patient profiles and monitored for safety and tolerability.

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