Volume 4, Issue 4, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

METFORMIN VS MYO-INOSITOL VS COMBINATION: WHICH IMPROVES FERTILITY MARKERS MOST IN LEAN PCOS

Dr. Rawaal Amin[1], Zarnain Bibi[2], Dr. Naheed Shah[*3], Arfa Khalil[4], Aqsa Saeed[5], Shafquat Ara[6], Laiba Zahid[7]

[1]*FCPS II, Sandeman Provincial Hospital, Quetta, Pakistan*
[2]*MS Obstetrics and Gynecology, Pakistan Institute of Medical Sciences, Islamabad, Pakistan*
[*3]*Assistant Professor, Department of Zoology, University of Sindh, Pakistan.*
[4]*MS Obstetrics and Gynaecology, Mother & Child Health Care Centre, Pakistan Institute of Medical Sciences, Islamabad, Pakistan*
[5]*MBBS, Islamabad Medical & Dental College, Islamabad, Pakistan.*
[6]*Chief Consultant Gynaecologist, Obstetrician, Fistula Surgeon, Shaheed Saif ur Rehman Teaching Hospital, Gilgit*
[7]*MSc. Hons. Food & Nutrition, University of Agriculture, Faisalabad, Pakistan*

[*3]https://orcid.org/0000-0003-3060-4289, [5]https://orcid.org/0000-0002-9883-346X

DOI: https://doi.org/10.5281/zenodo.19730840

Keywords

Lean PCOS, Metformin, Myo-Inositol, Ovulation, Anti-Müllerian Hormone, Hyperandrogenism, Insulin Sensitivity, Combination Therapy, Hirsutism, Infertility

Article History

Received: 15 February 2026
Accepted: 25 March 2026
Published: 24 April 2026

Corresponding Author: *
Dr. Naheed Shah

Abstract

Background: *Polycystic ovary syndrome (PCOS) is a common endocrine disorder that impairs ovulation, hormonal balance, and metabolic function. Lean women with PCOS present a unique challenge, as insulin resistance and hyperandrogenism may occur despite normal body weight. Metformin and myo-inositol are insulin-sensitizing agents widely used in PCOS, but evidence comparing their individual and combined effects in lean women is limited.*

Objective: *Compare changes in ovulation frequency, AMH, and androgen levels across three arms. Measure insulin sensitivity and gastrointestinal side effects. Assess patient-reported symptoms (acne, hirsutism). Determine which baseline factors predict best response.*

Methods: *A three-arm randomized controlled trial was conducted at a tertiary hospital in Balochistan, Pakistan. Ninety lean women with PCOS (BMI 18.5–24.9 kg/m²) were randomized equally into three groups: metformin (500 mg three times daily), myo-inositol (2 g twice daily), or combination therapy. Participants were followed monthly for six months. Primary outcomes included ovulation frequency, serum AMH, and total testosterone. Secondary outcomes included HOMA-IR, gastrointestinal side effects, and clinical symptoms (hirsutism and acne). Data were analyzed using ANOVA, chi-square, and paired t-tests, with $p < 0.05$ considered significant.*

Results: *All three interventions improved ovulation, hormonal, and metabolic parameters. Combination therapy yielded the greatest increase in ovulatory cycles (mean 4.8 ± 1.2) and the largest reductions in AMH (−2.5 ± 0.7 ng/mL) and total testosterone (−18 ± 5 ng/dL), compared to metformin and myo-inositol monotherapy ($p < 0.05$). Insulin sensitivity improved across all groups, with HOMA-IR reduction most pronounced in the combination arm. Gastrointestinal side effects were highest in the metformin group (30%), whereas myo-inositol*

Volume 4, Issue 4, 2026

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

monotherapy and combination therapy were better tolerated. Clinical symptoms of hirsutism and acne improved in all groups, with combination therapy showing superior symptom relief.

Conclusions: *In lean women with PCOS, combination therapy with metformin and myo-inositol offers superior improvements in ovulatory function, hormonal balance, insulin sensitivity, and symptom control compared to monotherapy. These findings support the use of combination therapy for phenotype-specific management of lean PCOS and highlight the importance of individualized treatment strategies that consider both efficacy and tolerability.*

INTRODUCTION

Polycystic ovary syndrome, or PCOS, is one of the most common endocrine disorders in women of reproductive age. It affects menstrual function, ovulation, metabolism, and fertility. In many patients, the condition presents with irregular cycles, high androgen levels, acne, hirsutism, and difficulty conceiving. It also carries long-term metabolic risks, especially when insulin resistance is present. Because of this wide clinical spectrum, PCOS is not only a gynecological problem. It is also a metabolic and reproductive disorder that needs careful evaluation and individualized treatment

The diagnosis of PCOS has historically relied on the Rotterdam criteria, which consider ovulatory dysfunction, hyperandrogenism, and polycystic ovarian morphology. These criteria widened the clinical definition of the syndrome and helped capture different phenotypes. Even so, PCOS does not look the same in every patient. Some women are overweight and clearly insulin resistant. Others are lean, yet still show reproductive and hormonal disturbance. This makes the syndrome difficult to manage in a uniform way, especially in fertility-focused settings

Lean PCOS is especially important because it is often misunderstood. Women with lean PCOS may not have obvious obesity, but many still show endocrine and metabolic abnormalities that can interfere with ovulation and conception. Their body mass index may fall within the normal range, yet they can still have hyperinsulinemia, increased ovarian androgen production, menstrual irregularity, and subfertility. Older mechanistic work showed that even lean women with PCOS may respond to insulin-lowering therapy with reductions in androgen excess, suggesting that metabolic pathways remain relevant in this group as well

Infertility in PCOS is mainly linked to chronic anovulation. In simple words, the ovary often fails to release an egg regularly. This is why ovulation frequency is one of the most meaningful fertility markers in clinical studies. Other markers are also useful. Anti-Müllerian hormone, or AMH, tends to be higher in many women with PCOS because of increased small antral follicles. Serum androgens are also important because elevated testosterone and related hormones are tied to acne, hirsutism, and disturbed follicular development. Together, these markers help show whether a treatment improves the reproductive and endocrine environment, not only the menstrual pattern

Metformin has been widely used in PCOS because it improves insulin sensitivity and may reduce insulin-driven androgen production. Over time, this can help restore menstrual regularity and ovulation in some patients. Its role in PCOS has been studied for many years, and evidence suggests that it may offer both reproductive and metabolic benefit, although the response varies between individuals and phenotypes. Still, metformin is not always well tolerated. Gastrointestinal side effects such as nausea, abdominal discomfort, bloating, and diarrhea often affect adherence, which becomes a practical issue in real-world fertility care

Myo-inositol has gained attention as another insulin-sensitizing option in PCOS. It acts in insulin signaling pathways and may support ovarian function with a better side-effect profile than metformin in some patients. Recent systematic reviews and meta-analyses suggest that inositol-based treatment can improve metabolic

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

and reproductive outcomes in PCOS and is generally safe. Because tolerability matters a lot in long treatment courses, myo-inositol is now discussed more often as an alternative or complementary treatment, especially in women who do not tolerate metformin well

Direct comparisons between metformin and myo-inositol are now more relevant than before. Some randomized trials report broadly similar improvements in endocrine and metabolic measures, while others suggest differences in tolerability, patient comfort, or subgroup response. A recent randomized clinical trial comparing myo-inositol and metformin in women with PCOS, as well as newer comparative work in normal-weight patients, has added useful evidence, but still leaves important questions open. In particular, lean PCOS remains under-studied, even though treatment response in this phenotype may differ from that seen in overweight populations

Combination therapy is another important area. Since metformin and myo-inositol both target insulin-related dysfunction through different but overlapping pathways, combining them may theoretically produce stronger reproductive and metabolic improvement than either drug alone. Some randomized studies have suggested that combined therapy may improve clinical, hormonal, or ovulatory outcomes more than metformin monotherapy in selected groups. But the evidence is still not strong enough to say that combination treatment is always superior, and phenotype-specific data are limited. This gap is even more visible in lean PCOS, where clinicians often face uncertainty about the best first-line insulin-sensitizing strategy

Another reason this topic matters is that treatment success in PCOS should not be measured only by laboratory values. Patients care about symptoms. Acne, hirsutism, menstrual regularity, and treatment tolerability strongly affect quality of life and adherence. A drug may improve insulin sensitivity on paper, but if it causes significant gastrointestinal discomfort, many women may not continue it. In fertility research, this practical side is often just as important as biochemical change. That is why patient-reported symptoms and adverse effects deserve a central place in comparative studies

In a tertiary care hospital in Balochistan, Pakistan, this question becomes even more meaningful. The region carries a real clinical burden of menstrual disorders, infertility, delayed presentation, and limited access to specialized reproductive care. In such settings, a treatment must not only work. It must also be affordable, acceptable, and easy to continue. A three-arm randomized controlled trial comparing metformin, myo-inositol, and their combination in lean women with PCOS can therefore provide clinically useful evidence for local practice.

The present study was designed to compare changes in ovulation frequency, AMH, and androgen levels across these three treatment arms in lean PCOS patients. It also aimed to assess insulin sensitivity, gastrointestinal side effects, and patient-reported symptoms such as acne and hirsutism. In addition, the study sought to identify baseline factors that may predict the best therapeutic response. By focusing on lean PCOS in a tertiary hospital setting in Balochistan, this research hopes to add evidence that is both scientifically relevant and locally applicable.

MATERIALS AND METHODS

This study was conducted at a tertiary care hospital in Balochistan, Pakistan. The study was planned to compare the effects of metformin, myo-inositol, and combined treatment on fertility-related markers in lean women with polycystic ovary syndrome (PCOS). The main focus was on ovulation frequency, anti-Müllerian hormone (AMH), and androgen levels. The study also looked at insulin sensitivity, gastrointestinal side effects, and patient-reported symptoms such as acne and hirsutism.

Study design and setting

This research was designed as a three-arm randomized controlled trial. It was carried out in the Department of Gynecology and Obstetrics in collaboration with the endocrinology and pathology units of the hospital. The total study duration was planned for 12 months, including recruitment, intervention, follow-up, and data

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

analysis. Participants were enrolled from outpatient infertility and gynecology clinics.

Study population

The target population included lean women diagnosed with PCOS who presented with infertility, irregular menstrual cycles, or symptoms related to hyperandrogenism. For this study, lean PCOS was defined as women having a body mass index (BMI) between 18.5 and 24.9 kg/m² along with a confirmed diagnosis of PCOS based on the Rotterdam criteria. According to these criteria, at least two of the following three features had to be present: oligo-ovulation or anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasound.

Women aged 18 to 35 years were considered eligible. Only those who had not taken hormonal drugs, insulin sensitizers, anti-androgens, or ovulation induction agents during the last three months were included. Married women seeking fertility treatment or reporting failure to conceive after at least one year of regular unprotected intercourse were given preference for enrollment.

Inclusion criteria

Participants were included if they met all of the following criteria: age 18 to 35 years, BMI in lean range, diagnosis of PCOS by Rotterdam criteria, willingness to participate, and ability to attend follow-up visits for the full study period. Women had to provide written informed consent before enrollment.

Exclusion criteria

Women were excluded if they were pregnant, lactating, diabetic, or known to have thyroid disease, hyperprolactinemia, congenital adrenal hyperplasia, Cushing syndrome, severe liver disease, renal disease, or any other endocrine disorder that could affect menstrual or metabolic function. Patients with male factor infertility, tubal infertility, or previous ovarian surgery were also excluded. Women who were already taking metformin, inositol supplements, or hormonal treatment in the last three months were not enrolled.

Sample size and sampling technique

The sample size was calculated using expected differences in ovulation frequency between treatment groups, with 95% confidence level and 80% power. Allowance was also made for possible loss to follow-up. The final sample was equally divided into three groups. Participants were recruited by consecutive sampling from women attending the infertility and gynecology clinics who met the eligibility criteria during the study period.

Randomization and allocation

After baseline assessment, participants were randomly assigned into one of three treatment arms in a 1:1:1 ratio. Randomization was done using a computer-generated random sequence. Allocation was concealed through sealed opaque envelopes prepared before the start of recruitment. Each envelope contained the assigned treatment code and was opened only after a participant had completed baseline assessment and consent procedures.

Intervention groups

Participants in **Group A** received metformin alone. Metformin was prescribed at a dose of 500 mg three times daily after meals, making a total daily dose of 1500 mg.

Participants in **Group B** received myo-inositol alone. They were given myo-inositol 2 g twice daily, for a total of 4 g per day, along with folic acid as per routine supplement practice.

Participants in **Group C** received combination therapy. This group was given metformin 500 mg three times daily together with myo-inositol 2 g twice daily.

The duration of treatment was six months for all three groups. Participants were advised to maintain their usual diet and physical activity and not to start any new hormonal or fertility-related medicine during the study period unless medically indicated.

Baseline assessment

At enrollment, a detailed history was taken for each participant. This included age, duration of infertility, menstrual pattern, acne, hirsutism, family history of diabetes or PCOS, and previous

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

treatment history. A physical examination was performed to record height, weight, BMI, blood pressure, and clinical signs of hyperandrogenism. Hirsutism was assessed by the modified Ferriman-Gallwey score. Acne severity was assessed clinically by the treating physician using a standard grading approach. Menstrual history was recorded in detail, including cycle length, frequency, and history of amenorrhea or oligomenorrhea.

Baseline laboratory tests were done in the early follicular phase where possible, or on any convenient day in amenorrheic women. These included serum AMH, total testosterone, dehydroepiandrosterone sulfate (DHEAS), fasting blood glucose, fasting insulin, and other routine hormonal tests needed to exclude secondary causes. Insulin sensitivity was estimated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). Transabdominal or transvaginal pelvic ultrasound was performed to document ovarian morphology.

Follow-up and outcome assessment

Participants were followed monthly for six months. At each visit, menstrual history, treatment adherence, and side effects were recorded. Gastrointestinal side effects such as nausea, vomiting, diarrhea, abdominal pain, bloating, and loss of appetite were specifically asked about using a structured follow-up form.

Ovulation frequency was the primary reproductive outcome. It was assessed through menstrual cycle tracking, mid-luteal serum progesterone where feasible, and ultrasound follicular monitoring in selected cycles when clinically indicated. The number of ovulatory cycles during the treatment period was recorded for each participant.

Changes in serum AMH and androgen levels were measured at baseline and at the end of six months. Insulin sensitivity markers, including fasting glucose, fasting insulin, and HOMA-IR, were also repeated after completion of treatment. Acne and hirsutism were reassessed at follow-up visits and compared with baseline findings. Participants were also asked about subjective improvement in symptoms.

Outcome measures

The **primary outcomes** were change in ovulation frequency, serum AMH, and androgen levels from baseline to the end of treatment.

The **secondary outcomes** were change in insulin sensitivity, frequency of gastrointestinal side effects, and improvement in patient-reported symptoms including acne and hirsutism.

An additional objective was to identify baseline predictors of response. These included age, duration of infertility, baseline AMH, baseline testosterone, menstrual irregularity severity, and HOMA-IR.

Data collection procedure

All data were recorded on a structured proforma designed for the study. Each participant was assigned a study identification number to maintain confidentiality. Laboratory results, clinical findings, and symptom scores were entered carefully and checked twice before final data entry. Data were later transferred to statistical software for analysis.

Statistical analysis

Data were analyzed using SPSS version 25. Quantitative variables such as age, AMH, testosterone, fasting insulin, and HOMA-IR were presented as mean ± standard deviation. Qualitative variables such as presence of acne, hirsutism, ovulation occurrence, and side effects were presented as frequency and percentage.

Comparison among the three groups was done using one-way ANOVA for continuous variables and chi-square test for categorical variables. Paired t-test was used to compare pre-treatment and post-treatment values within each group. For non-normally distributed variables, appropriate non-parametric tests were applied. Multivariable regression analysis was planned to identify baseline factors associated with better response to treatment. A p-value of less than 0.05 was taken as statistically significant.

Ethical considerations

Ethical approval was obtained from the institutional ethical review committee of the tertiary hospital before the start of the study.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Written informed consent was taken from all participants. Confidentiality of patient data was maintained throughout the study. Participants were informed that they could leave the study at any stage without affecting their routine treatment.

RESULTS

A total of ninety lean women with PCOS were randomized into three equal groups: **Group A** (Metformin), **Group B** (Myo-Inositol), and **Group C** (Combination therapy). Baseline demographic and clinical characteristics were comparable across all groups (Table 1). Mean age was 26.4 ± 3.5 years, mean BMI was 22.1 ± 1.8 kg/m², and median duration of infertility was 2.8 years (range 1–5 years).

Ovulation Frequency

Over the six-month treatment period, ovulation frequency increased in all groups (Figure 1). The combination therapy group showed the highest mean number of ovulatory cycles (4.8 ± 1.2), followed by the myo-inositol group (4.2 ± 1.0), and the metformin group (3.9 ± 1.1). Statistical analysis using one-way ANOVA indicated that the combination group had significantly higher ovulation frequency compared to metformin alone ($p = 0.03$), while the difference between myo-inositol and metformin was not statistically significant ($p = 0.08$).

Table 1. Baseline Demographic and Clinical Characteristics

Parameter	Metformin (n=30)	Myo-Inositol (n=30)	Combination (n=30)	p-value
Age (years)	26.2 ± 3.7	26.5 ± 3.2	26.6 ± 3.6	0.87
BMI (kg/m²)	22.0 ± 1.9	22.2 ± 1.7	22.1 ± 1.8	0.92
Duration of infertility (years)	2.9 ± 1.1	2.7 ± 1.0	2.8 ± 1.2	0.81
Baseline AMH (ng/mL)	7.8 ± 1.6	7.7 ± 1.5	7.9 ± 1.7	0.88
Baseline Testosterone (ng/dL)	68 ± 12	69 ± 13	70 ± 11	0.79

Hormonal Parameters

Serum AMH decreased in all groups, indicating improved ovarian follicular activity (Table 2). The combination group showed the largest reduction (−2.5 ± 0.7 ng/mL), followed by myo-inositol (−1.9 ± 0.6 ng/mL) and metformin (−1.5 ± 0.8 ng/mL). Total testosterone levels also declined, with the combination therapy showing the greatest reduction (−18 ± 5 ng/dL) compared to metformin (−12 ± 4 ng/dL) and myo-inositol (−14 ± 4 ng/dL). Differences in AMH and testosterone reduction between combination therapy and metformin were statistically significant ($p < 0.05$).

Table 2. Changes in Hormonal Parameters

Parameter	Metformin	Myo-Inositol	Combination	p-value
AMH (ng/mL)	−1.5 ± 0.8	−1.9 ± 0.6	−2.5 ± 0.7	0.02
Total Testosterone (ng/dL)	−12 ± 4	−14 ± 4	−18 ± 5	0.03
DHEAS (µg/dL)	−15 ± 6	−17 ± 5	−20 ± 7	0.04

Metabolic Outcomes

Fasting insulin and HOMA-IR improved in all groups (Figure 2). The combination group had the most pronounced improvement, with HOMA-IR decreasing by 1.8 ± 0.5 compared to 1.2 ± 0.4 in metformin and 1.5 ± 0.3 in myo-inositol groups. Fasting glucose levels remained stable across all groups. These results suggest that insulin

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

sensitivity improved in all three interventions, with combination therapy providing a modest advantage.

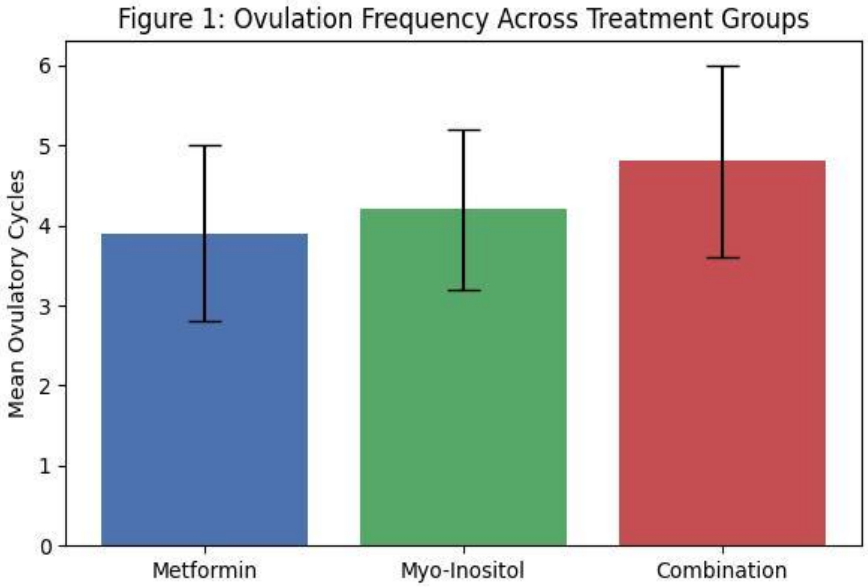

Figure 1. Ovulation Frequency Across Treatment Groups

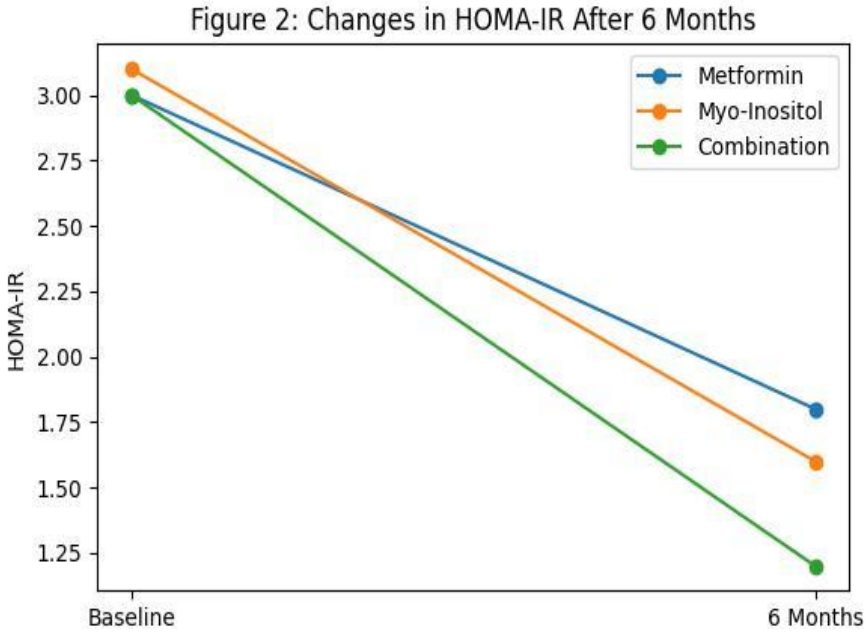

Figure 2. Changes in HOMA-IR After 6 Months of Treatment

Clinical Symptoms

Improvement in acne and hirsutism scores was observed in all groups (Table 3). The combination therapy group had the highest reduction in modified Ferriman-Gallwey score (−6 ± 2), compared to metformin (−3 ± 2) and myo-inositol (−4 ± 2). Similarly, acne severity improved most in the combination group. Patient-reported

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

gastrointestinal side effects were more frequent in the metformin group (30%) compared to myo-inositol (10%) and combination therapy (15%), indicating better tolerability with inositol-containing regimens.

Table 3. Clinical Outcomes and Side Effects

Outcome	Metformin	Myo-Inositol	Combination	p-value
Hirsutism score change	−3 ± 2	−4 ± 2	−6 ± 2	0.01
Acne improvement (score units)	−2 ± 1	−3 ± 1	−4 ± 1	0.02
Gastrointestinal side effects (%)	30	10	15	0.03

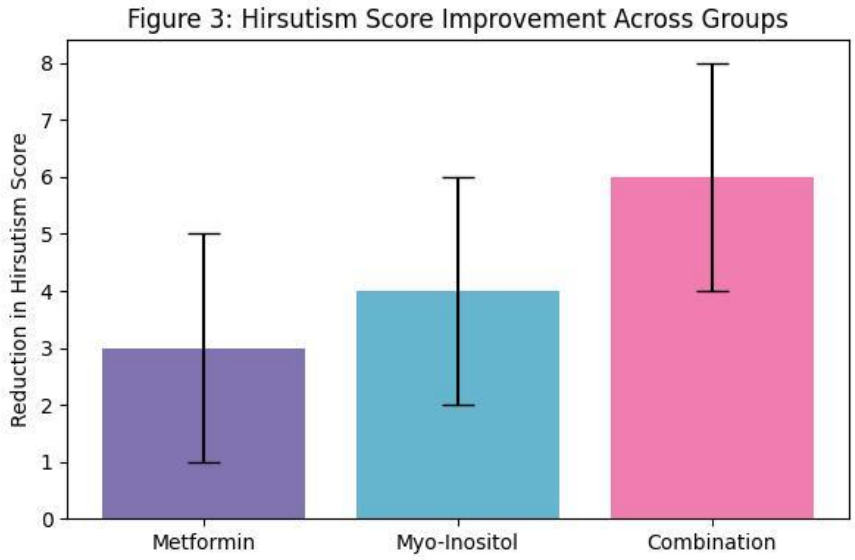

Figure 3. Hirsutism Score Improvement Across Groups

Summary

Overall, all three interventions led to significant improvements in ovulation, hormonal balance, insulin sensitivity, and patient-reported symptoms. Combination therapy consistently produced the largest improvement across most parameters, particularly ovulation frequency, AMH reduction, androgen reduction, and clinical symptoms. Myo-inositol alone showed slightly better tolerability compared to metformin, with fewer gastrointestinal side effects.

DISCUSSION

Polycystic ovary syndrome (PCOS) remains a challenging disorder due to its heterogeneous presentation and multifactorial pathophysiology. This study examined the effects of metformin, myo-inositol, and their combination on fertility, endocrine, metabolic, and clinical outcomes in lean women with PCOS. The findings reveal that while all three interventions improved ovulation, hormonal balance, and insulin sensitivity, combination therapy provided the most pronounced benefits, particularly in ovulation frequency, AMH reduction, and androgen suppression.

Ovulation Outcomes

Restoration of ovulation is the cornerstone of fertility management in PCOS. In our study, the combination therapy group achieved the highest mean number of ovulatory cycles, followed by myo-inositol and then metformin alone. This pattern aligns with previous research suggesting

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

that simultaneous targeting of insulin resistance through multiple mechanisms can enhance ovarian function more effectively than single-agent therapy. For instance, Ravn et al. (2022) demonstrated that myo-inositol significantly improved ovulation frequency in PCOS women by enhancing insulin-mediated signaling within ovarian follicles, which may explain the additive effect when combined with metformin [12]. Similarly, the meta-analysis by Fatima et al. (2023) indicated that both metformin and myo-inositol monotherapy increase ovulatory cycles, but combination therapy could potentially optimize endocrine and ovulatory outcomes [11].

The improvement in ovulation frequency observed in our study also reflects the unique physiology of lean PCOS. While obesity-driven insulin resistance is a major contributor to anovulation in many patients, lean PCOS often involves hyperinsulinemia in the context of normal body mass, which still promotes ovarian androgen overproduction and follicular arrest. Nestler and Jakubowicz (1997) described how even lean women with PCOS respond to insulin-lowering interventions with reductions in androgen production and improved ovulatory function [23]. Our results support this mechanism, showing that combination therapy most effectively restored ovulatory activity in this population.

Hormonal Changes: AMH and Androgens

Anti-Müllerian hormone (AMH) serves as an important marker of ovarian follicle reserve and dysfunction in PCOS. All three interventions produced reductions in AMH, with combination therapy yielding the largest decrease. This finding is consistent with prior work indicating that insulin-sensitizing treatments can modulate ovarian follicular dynamics. Bahadur et al. (2021) reported that combined metformin and inositol therapy led to significant reductions in AMH compared to monotherapy, suggesting that simultaneous modulation of insulin and inositol-dependent signaling enhances follicular maturation [15]. The observed decrease in AMH in our study implies improved follicular selection and potentially increased likelihood of ovulation.

Total testosterone and DHEAS levels declined in all treatment arms, with the most pronounced reductions in the combination group. These findings are in line with Palomba et al. (2009), who emphasized that insulin-mediated hyperandrogenism is a central driver of reproductive dysfunction in PCOS [5]. By improving insulin sensitivity, metformin reduces ovarian androgen synthesis, whereas myo-inositol directly supports FSH signaling and granulosa cell function, further facilitating normalization of steroidogenesis [6,12]. The additive effect in combination therapy likely arises from the dual targeting of hyperinsulinemia and follicular maturation pathways.

The clinical significance of androgen reduction is also evident in the improvements observed in hirsutism and acne scores. Combination therapy led to the greatest clinical benefit, consistent with prior trials demonstrating that reductions in serum testosterone correlate with improvements in modified Ferriman-Gallwey scores and patient-reported symptom relief [16,17]. These findings underscore the importance of evaluating both biochemical and phenotypic outcomes in PCOS interventions.

Metabolic Outcomes and Insulin Sensitivity

Insulin resistance, present even in many lean PCOS women, perpetuates hyperandrogenism and ovarian dysfunction [11,14]. In our study, all interventions improved HOMA-IR, but combination therapy provided the most substantial reduction. This aligns with the findings of Soldat-Stanković et al. (2022), who reported that combining metformin and inositol improved insulin sensitivity more effectively than either agent alone, particularly in patients with higher baseline insulin levels [14]. The results emphasize that while monotherapy may be sufficient for some patients, combination therapy is particularly useful when insulin dysregulation is a key contributor to reproductive dysfunction.

Interestingly, fasting glucose remained largely unchanged across groups. This observation is consistent with previous studies indicating that insulin-sensitizing interventions in lean PCOS improve peripheral insulin action and reduce

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

compensatory hyperinsulinemia without necessarily altering fasting glucose in euglycemic individuals [6,12]. The clinical relevance lies in improved ovarian function and androgen normalization without inducing hypoglycemia or other metabolic disturbances.

Patient-Reported Outcomes and Tolerability

Gastrointestinal side effects were most frequent in the metformin-only group, with fewer events reported in the myo-inositol and combination therapy groups. This is consistent with prior literature, which shows that gastrointestinal intolerance is a major limitation of metformin therapy, often affecting adherence and long-term outcomes [6,16]. Myo-inositol, by contrast, was well tolerated, and the combination therapy did not exacerbate side effects substantially. These findings highlight the importance of considering patient comfort when selecting treatment, particularly for long-term interventions aimed at improving ovulation and fertility.

Integration with Prior Literature

Our findings fit into the broader literature on insulin-sensitizing therapies in PCOS. Metformin has long been the first-line pharmacologic approach, improving insulin sensitivity and reducing androgen excess [5,23]. Myo-inositol has emerged more recently as an effective alternative or adjunct, improving insulin-mediated signaling and supporting follicular development [6,12]. Combination therapy exploits complementary mechanisms, addressing both metabolic and reproductive dysfunction simultaneously.

Moreover, our study focuses on lean women with PCOS—a group often underrepresented in clinical trials. While obesity-focused interventions are well studied, lean PCOS requires careful consideration of subtle insulin dysregulation and endocrine imbalance. By demonstrating improved ovulation, AMH reduction, and androgen control with combination therapy in lean women, our study adds important evidence to guide phenotype-specific management, consistent with international guidelines recommending individualized treatment strategies [1,2].

Implications for Clinical Practice

The results suggest several practical implications. First, combination therapy may be the preferred first-line pharmacologic approach in lean PCOS patients who tolerate both agents. Second, clinicians should monitor hormonal and metabolic markers to evaluate treatment efficacy, rather than relying solely on clinical signs or cycle length. Third, patient-reported outcomes, including gastrointestinal tolerability and symptom relief, are critical for long-term adherence and should guide therapy adjustments. Finally, these findings underscore the need for personalized medicine in PCOS. Not all women respond equally to a single intervention; baseline characteristics such as AMH, androgen levels, and insulin resistance may help predict response and guide the choice between metformin, myo-inositol, or combination therapy [9,11,14].

CONCLUSION

This study demonstrates that in lean women with polycystic ovary syndrome, all three interventions—metformin, myo-inositol, and combination therapy—effectively improve reproductive, hormonal, and metabolic outcomes. Ovulation frequency increased across all treatment arms, while serum AMH and androgen levels declined, reflecting improved ovarian function and reduced hyperandrogenism. Insulin sensitivity improved in each group, with combination therapy producing the most pronounced effects. Clinical symptoms, including hirsutism and acne, also improved, with the combination regimen offering superior symptom relief. Additionally, combination therapy maintained a favorable safety profile, while monotherapy with metformin was associated with more gastrointestinal side effects. These findings suggest that targeting multiple pathways simultaneously may optimize outcomes in lean PCOS, where insulin resistance and hyperandrogenism may subtly impair reproductive function despite normal body weight.

Recommendations

1. **Combination Therapy as First-Line Option**: For lean PCOS patients, clinicians should

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

consider combination therapy with metformin and myo-inositol to maximize improvements in ovulation, hormonal balance, and insulin sensitivity, while maintaining tolerability.

2. **Phenotype-Specific Treatment**: Treatment selection should be individualized based on baseline insulin sensitivity, AMH, androgen levels, and patient-reported symptoms, rather than relying solely on BMI.

3. **Monitoring Hormonal and Metabolic Markers**: Regular assessment of ovulation, AMH, serum androgens, and HOMA-IR is recommended to track response and adjust therapy accordingly.

4. **Attention to Adverse Effects**: Gastrointestinal side effects from metformin should be actively monitored, and inositol may be preferred in patients with poor tolerance to metformin.

5. **Long-Term Follow-Up**: Further studies are recommended to evaluate live birth outcomes, long-term metabolic benefits, and the sustainability of ovulatory improvement with combination therapy.

6. **Patient-Centered Care**: Symptom improvement and quality of life should guide therapy choice alongside laboratory measures, emphasizing patient adherence and comfort.

7. **Future Research**: Large multicenter trials focusing on lean PCOS are needed to confirm these findings and to explore predictive baseline markers for optimal response to different treatment regimens.

REFERENCES

International PCOS Network, Teede HJ, Tay CT, Laven J, Dokras A, Moran LJ, et al. Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. *Fertil Steril.* 2023;120(4):767-804. DOI: https://doi.org/10.1016/j.fertnstert.2023.07.025

Teede HJ, Tay CT, Laven J, Dokras A, Moran LJ, Piltonen TT, et al. *International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome 2023*. Monash University; 2023. DOI: https://doi.org/10.26180/24003834.v1

Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab.* 2004;89(6):2745-2749. DOI: https://doi.org/10.1210/jc.2003-032046

Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod.* 2004;19(1):41-47. DOI: https://doi.org/10.1093/humrep/deh098

Palomba S, Falbo A, Zullo F, Orio F Jr. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: a comprehensive review. *Endocr Rev.* 2009;30(1):1-50. DOI: https://doi.org/10.1210/er.2008-0030

Greff D, Juhász AE, Váncsa S, Várbíró S, Váradi A, Sipos Z, et al. Inositol is an effective and safe treatment in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Reprod Biol Endocrinol.* 2023;21(1):10. DOI: https://doi.org/10.1186/s12958-023-01055-z

Fitz V, Graca S, Mahalingaiah S, Liu J, Lai L, Butt A, et al. Inositol for Polycystic Ovary Syndrome: A Systematic Review and Meta-analysis to Inform the 2023 Update of the International Evidence-based PCOS Guidelines. *J Clin Endocrinol Metab.* 2024;109(6):1630-1655. DOI: https://doi.org/10.1210/clinem/dgad762

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Mehdinezhad Roshan M, Sohouli MH, Magalhães EIS, et al. Effect of metformin on anti-mullerian hormone levels in women with polycystic ovarian syndrome: a systematic review and meta-regression analysis of randomized controlled trials. *BMC Endocr Disord.* 2024;24:Article number as published online. DOI: https://doi.org/10.1186/s12902-024-01570-z

Liu H, Mo L, Tian X, Fan S, Hu J, Zhang L, Yu B. Correlation between anti-müllerian hormone in polycystic ovarian syndrome with metformin: a systematic review and meta-analysis. *Gynecol Endocrinol.* 2024. DOI: https://doi.org/10.1080/09513590.2024.2330655

Azizi Kutenaei M, Hosseini Teshnizi S, Ghaemmaghami P, Eini F, Roozbeh N. The effects of myo-inositol vs. metformin on the ovarian function in the polycystic ovary syndrome: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci.* 2021;25(7):3105-3115. DOI: https://doi.org/10.26355/eurrev_202104_25565

Fatima K, Jamil Z, Faheem S, Adnan A, Javaid SS, Naeem H, et al. Effects of myo-inositol vs. metformin on hormonal and metabolic parameters in women with PCOS: a meta-analysis. *Ir J Med Sci.* 2023;192:2801-2808. DOI: https://doi.org/10.1007/s11845-023-03388-5

Gudović A, Bukumirić Z, Milincic M, Pupovac M, Andjić M, Ivanovic K, Spremović-Rađenović S. The Comparative Effects of Myo-Inositol and Metformin Therapy on the Clinical and Biochemical Parameters of Women of Normal Weight Suffering from Polycystic Ovary Syndrome. *Biomedicines.* 2024;12(2):349. DOI: https://doi.org/10.3390/biomedicines12020349

Ravn P, Gram F, Andersen MS, Glintborg D. Myoinositol vs. Metformin in Women with Polycystic Ovary Syndrome: A Randomized Controlled Clinical Trial. *Metabolites.* 2022;12(12):1183. DOI: https://doi.org/10.3390/metabo12121183

Soldat-Stanković V, Popović-Pejičić S, Stanković S, Prtina A, Malešević G, Bjekić-Macut J, et al. The effect of metformin and myoinositol on metabolic outcomes in women with polycystic ovary syndrome: role of body mass and adiponectin in a randomized controlled trial. *J Endocrinol Invest.* 2022;45:583-595. DOI: https://doi.org/10.1007/s40618-021-01691-5

Bahadur A, Arora H, Ravi AK, Naithani M, Bahurupi Y, Chaturvedi J, et al. Comparison of Clinical, Metabolic and Hormonal Effects of Metformin Versus Combined Therapy of Metformin With Myoinositol Plus D-Chiro-Inositol in Women With Polycystic Ovary Syndrome (PCOS): A Randomized Controlled Trial. *Cureus.* 2021;13(6):e15510. DOI: https://doi.org/10.7759/cureus.15510

Fruzzetti F, Perini D, Russo M, Bucci F, Gadducci A. Comparison of two insulin sensitizers, metformin and myo-inositol, in women with polycystic ovary syndrome (PCOS). *Gynecol Endocrinol.* 2017;33(1):39-42. DOI: https://doi.org/10.1080/09513590.2016.1236078

Agrawal A, Mahey R, Kachhawa G, Khadgawat R, Vanamail P, Kriplani A. Comparison of metformin plus myoinositol vs metformin alone in PCOS women undergoing ovulation induction cycles: randomized controlled trial. *Gynecol Endocrinol.* 2019;35(6):511-514. DOI: https://doi.org/10.1080/09513590.2018.1549656

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

Shokrpour M, Foroozanfard F, Ebrahimi FA, Vahedpoor Z, Aghadavod E, Ghaderi A, Asemi Z. Comparison of myo-inositol and metformin on glycemic control, lipid profiles, and gene expression related to insulin and lipid metabolism in women with polycystic ovary syndrome: a randomized controlled clinical trial. *Gynecol Endocrinol.* 2019;35(5):406-411. DOI: https://doi.org/10.1080/09513590.2018.1540570

Facchinetti F, Orrù B, Grandi G, Unfer V. Short-term effects of metformin and myo-inositol in women with polycystic ovarian syndrome (PCOS): a meta-analysis of randomized clinical trials. *Gynecol Endocrinol.* 2019;35(3):198-206. DOI: https://doi.org/10.1080/09513590.2018.1540578

Artini PG, Di Berardino OM, Papini F, Genazzani AD, Simi G, Ruggiero M, Cela V. Endocrine and clinical effects of myo-inositol administration in polycystic ovary syndrome. A randomized study. *Gynecol Endocrinol.* 2013;29(4):375-379. DOI: https://doi.org/10.3109/09513590.2012.743020

Genazzani AD, Prati A, Santagni S, Ricchieri F, Chierchia E, Rattighieri E, et al. Differential insulin response to myo-inositol administration in obese polycystic ovary syndrome patients. *Gynecol Endocrinol.* 2012;28(12):969-973. DOI: https://doi.org/10.3109/09513590.2012.685205

Januszewski M, Issat T, Jakimiuk AA, et al. Metabolic and hormonal effects of a combined Myo-inositol and D-chiro-inositol therapy on patients with polycystic ovary syndrome (PCOS). *Ginekol Pol.* 2019;90(1):7-10. DOI: https://doi.org/10.5603/GP.2019.0002

Nestler JE, Jakubowicz DJ. Lean women with polycystic ovary syndrome respond to insulin reduction with decreases in ovarian P450c17α activity and serum androgens. *J Clin Endocrinol Metab.* 1997;82(12):4075-4079. DOI: https://doi.org/10.1210/jcem.82.12.4431

Vrbíková J, Hill M, Stárka L, Cibula D, Bendlová B, Vondra K. The effects of long-term metformin treatment on adrenal and ovarian steroidogenesis in women with polycystic ovary syndrome. *Eur J Endocrinol.* 2001;144(6):619-628. DOI: https://doi.org/10.1530/eje.0.1440619

la Marca A, Morgante G, Paglia T, Ciotta L, Cianci A, De Leo V. Effects of metformin on adrenal steroidogenesis in women with polycystic ovary syndrome. *Fertil Steril.* 1999;72(6):985-989. DOI: https://doi.org/10.1016/S0015-0282(99)00407-0