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The Effects of Adjunctive Nimesulide on Androgen and Gonadotropin Profiles in Women with PCOS: A Controlled Clinical Study

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ABSTRACT

Background & Objective: Polycystic Ovary Syndrome (PCOS) features dysregulated gonadotropins and hyperandrogenism. The present study was conducted with aim to evaluate whether adding the selective COX-2 inhibitor nimesulide to metformin improves androgen and gonadotropin profiles versus metformin alone in women with PCOS.

Materials & Methods: This prospective controlled study was conducted on 100 reproductive-age women with PCOS who completed 3 weeks of therapy with either metformin alone (500 mg three timesdaily) or metformin plus nimesulide (100 mg twice daily). The participants recruited from the hospital and daily clinic in Basrah and Misan. The primary outcome was change in total and free testosterone, LH, FSH and secondary outcomes included Dehydroepiandrosterone Sulfate (DHEA-S), as well as selected inflammatory and lipid indices.

Results: Both groups showed significant reductions in total testosterone (P<0.001) and free testosterone (P=0.001) and LH (P<0.001), with greater improvements in the combination group. FSH increased significantly (P<0.001) after combination therapy. DHEA-S levels don't differ significantly in both groups (P=0.375). Post-treatment, FSH was significantly higher in the combination group (P=0.003), while other hormonal differences were not statistically significant.

Conclusion: Over 3 weeks, metformin improved androgen excess and gonadotropin imbalance in PCOS, and adjunctive nimesulide amplified within-group hormonal shifts and selectively increased FSH. These findings support short-course anti-inflammatory co-treatment to augment endocrine benefits of metformin and motivate longer randomized trials. Clinical endpoints warrant assessment over extended follow-up periods.

Keywords: Polycystic ovary syndrome, Metformin, Nimesulide, Female reproductive hormones, Hyperandrogenism

1. Introduction

Polycystic Ovary Syndrome (PCOS) involves dysregulation of the Hypothalamic-Pituitary-Ovarian (HPO) axis, notably an increased Gonadotropin-Releasing Hormone (GnRH) pulse frequency that leads to Luteinizing Hormone (LH) hypersecretion and a persistently elevated LH/Follicle-Stimulating Hormone (FSH) ratio **(1)**. This LH predominance disrupts folliculogenesis, causing follicular arrest, theca cell hyperplasia, and excess ovarian androgen production **(2)**. Impaired feedback from estradiol and progesterone-referred to as estrogen being one of the most common causes of progesterone deficiency, may further stimulate LH hypersecretion **(3)**. Metabolic issues like insulin resistance and hyperinsulinemia worsen this imbalance by increasing LH secretion and ovarian androgen sensitivity **(4)**. Adipokines also act on this axis, which contributes to the altered GnRH signaling **(5)**. Both ovarian and adrenal sources contribute to hyper androgens-elevated testosterone and DHEA-S are closely associated with LH dysregulation **(6)**. The condition is associated with a wide diversity of symptoms that comprise dysregulation of menstrual cycle, hyperandrogenism, and morphology of polycyclic ovaries, insulin resistance and sterility, obesity and insulin resistance. These occurrences do not only deteriorate reproductive capacity but also considerably aggravate the general metabolic, cardiovascular and psychological state of the affected women.

Metformin helps to improve gonadotropin balance in PCOS by improving insulin sensitivity and reducing cyclooxygenase-2 COX-2, which reduces LH hypersecretion and normalizes LH/FSH ratio **(7)**. Emerging data reveal that metformin has additional anti-inflammatory properties by diminishing gene expression of inflammation through the corresponding cascade of pathways such as inhibition of COX-2 and IL-1beta through the signaling system of the adenosine monophosphate-activated protein kinase (AMPK)/nuclear factor erythrocyte 2 (Nf2). As COX-2 overexpression interferes with hypothalamic-pituitary-ovarian signaling, it is a potential target in which selective COX-2 inhibitors such as nimesulide can be used **(8)**. Nimesulide is selective for COX-2 and in tumor models, reduces markers of angiogenesis, relevant in ovarian environments **(9)**. In combination, metformin and COX-2 inhibitors have a synergistic effect on oxidative stress and inflammatory cascades **(10)**. New nimesulide analogs possess high COX-2 selectivity, which provides refined therapeutic windows **(11)**. Clinically this dual approach could minimize LH, enhance FSH support, ameliorate testosterone and DHEA-S and increase ovulation, whereas short course nimesulide limits safety issues **(12)**.

The present study was designed to assess whether nimesulide supplementation of standard metformin therapy resulted in superior betterments of the hormonal milieu in women suffering with polycystic ovary syndrome when compared with metformin only. The primary goal was to assess the magnitude of reduction of the concentration of total testosterone and free testosterone in the blood over the course of treatment by combination therapy, in order to resolve the main feature of biochemical hyperandrogenism that defines the syndrome.

2. Materials and Methods

This prospective, case-controlled clinical trial study was conducted on 100 women with PCOS. The diagnosis of PCOS was based on the Rotterdam 2003 criteria, which require the presence of at least two of the following: oligo/anovulation, clinical or biochemical signs of hyperandrogenism, and polycystic ovarian morphology detected by ultrasound **(13)**. Participants were assigned to either a combination-therapy group or a metformin-only control group according to the applied therapeutic protocol. Randomization was not implemented due to clinical and logistical constraint, including the restricted number of eligible participants attending the study center within the defined timeframe and ethical considerations related to withholding anti-inflammatory treatment in symptomatic subjects, instead strict eligibility criteria were applied to enhance the internal validity. The intervention period spanned three weeks for each participant, a duration selected to detect pharmacodynamically plausible changes while limiting exposure to non-steroidal anti-inflammatory drugs.

The study was conducted in the hospital and outpatient clinics in the cities of Misan and Basrah, which provided access to diagnostic laboratories and trained personnel, enabling standardized assessments and on-site sample handling. Recruitment and follow-up were conducted over one calendar year to achieve the target sample size with flexible scheduling, while each participant completed a defined three-week treatment and assessment window.

The target population comprised women of reproductive age diagnosed with PCOS who attended the participating hospital and clinic services. A purposive sampling approach was used to enroll candidates who met the prespecified diagnostic and clinical stability requirements. Potential participants were identified during routine visits or via physician referral, counseled regarding the study, and screened through history, physical examination, and preliminary laboratory tests. Eligible women were allocated to the combination-therapy group (nimesulide plus metformin) or the metformin-only group, with sequential, balanced enrollment to preserve comparability.

Inclusion criteria were a clinical diagnosis of PCOS consistent with internationally accepted criteria, supported by menstrual irregularity and/or clinical or biochemical hyperandrogenism. Participants were within a defined reproductive age range (18-35 years), which represents the typical period of female fertility and active ovarian function **(14)**. All participants were clinically stable, and free of recent exposure to hormones or anti-inflammatory drugs during a wash-out period to ensure untreated baselines.

Exclusion criteria eliminated conditions that could confound the outcomes or pose safety risks, including diabetes mellitus, cardiovascular, renal, hepatic, or significant gastrointestinal disease. Endocrine disorders overlapping with PCOS (such as congenital adrenal hyperplasia, Cushing syndrome, or thyroid disease) were excluded, as were prior hormone-sensitive malignancies and active gynecologic cancers. Women with known hypersensitivity to NSAIDs or nimesulide, and pregnant, lactating, or actively conceiving women, were also excluded. Concomitant medications affecting metabolism or hormonal indices (e.g., corticosteroids, antiepileptics, anticoagulants, hormonal contraceptives, and other NSAIDs/COX-2 inhibitors) were not included in the study.

Eligible participants were assigned to two groups. The intervention group received nimesulide 100 mg twice daily in addition to a standard metformin regimen for three consecutive weeks. The control group received metformin 500mg three times daily alone. Adherence was reinforced through direct communication and scheduled follow-ups.

The lack of randomization and placebo control were due to both ethical and practical constraints, and the study was conducted in a real-world clinical setting where participants required active treatment for symptomatic PCOS. Preventing anti-inflammatory therapy or providing a placebo instead of an active drug was considered ethically inappropriate for women experiencing significant pelvic discomfort or inflammation-related symptoms. Additionally, logistical limitations, including the limited number of eligible participants and unavailability of matched placebo tablets, prevented the use of a randomized, placebo-controlled design. To minimize the selection bias, strict eligibility criteria and standardized treatment protocols were applied across both groups.

Sample size calculations targeted detection of a clinically meaningful difference in primary outcomes (serum testosterone) and key inflammatory markers between the groups. Using a two-sample mean comparison with α=0.05 and power 80%, and assuming a standard deviation of 0.6 ng/mL and a minimum detectable difference of 0.5 ng/mL, the required size was calculated as 23 per group. Allowing for attrition and protocol deviations, 50 participants were enrolled per group, yielding a total sample of 100.

Clinical data were collected using a structured interviewer-administered questionnaire capturing demographics, medical history, symptoms, and medication use. Clinical hyperandrogenism was assessed by the modified Ferriman-Gallwey (mFG) scoring system after standardized training to minimize inter-observer variability. Venous blood was collected via sterile venipuncture for laboratory analyses. Assay kits and platforms included a free testosterone ELISA (Cayman Chemical, Cat. No. 582701) and an IL-6 ELISA (Abcam, ab178013). COBAS immunoassay systems (e411, Roche Diagnostics) quantified Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), Dehydroepiandrosterone Sulfate (DHEA-S), C-Reactive Protein (CRP), and lipid parameters. A BioTek ELx800 microplate reader was used for ELISA absorbance; centrifugation and sample processing were supported by calibrated laboratory equipment (e.g., refrigerated centrifuge and -80 °C storage). Routine calibration, maintenance, and internal quality controls were performed per manufacturer and institutional protocols.

Blood samples were collected into serum-separator tubes, centrifuged at 3000×g for 10 minutes, and the serum aliquots were stored at -80 °C until analysis. DHEA-S was measured using automated chemiluminescent immunoassays. LH and FSH were measured by electrochemiluminescence immunoassay on the COBAS e411 platform. ELISA procedures followed standardized steps with reagents equilibrated to room temperature, freshly prepared standards and controls, and random assignment of samples to plates to mitigate batch effects. Four-parameter logistic calibration curves were generated, and blinded duplicates and control repeats were included in each run, maintaining inter-assay variability within predefined limits.

The primary outcome was the change in total serum testosterone from baseline to the end of the three-week intervention. Secondary endocrine outcomes included serum free testosterone, DHEA-S, LH, and FSH. Exploratory inflammatory outcomes included high-sensitivity CRP and IL-6 to characterize low-grade inflammation associated with PCOS and to explore potential links with hormonal changes.

Data was analyzed using Microsoft Excel for initial data handling and IBM SPSS Statistics (version 26) for inferential analyses. Descriptive statistics summarize baseline characteristics, means and standard deviations for continuous variables and counts and percentages for categorical variables. Baseline comparability was examined using independent-samples t-tests for normally distributed continuous variables and Within-group changes from baseline to post-treatment were analyzed using paired t-tests for normally distributed variables. Between-group comparisons focused on change scores (Δ-values) using independent-samples t-tests or Mann-Whitney U tests as appropriate. Effect sizes (Cohen's d) and 95% confidence intervals were calculated for primary outcomes. Multiple comparisons in post hoc analyses of hormonal variables were controlled using Bonferroni adjustments. Relationships between inflammatory and hormonal changes were explored with Pearson correlations for normal data and Spearman rank correlations otherwise. A linear regression model evaluated whether baseline CRP predicted subsequent changes in testosterone. Outliers were assessed via standardized residuals and boxplots; retention or exclusion was based on clinical plausibility and measurement verification. Analyses adhered to an intention-to-treat framework for participants who completed the protocol, with no imputation required for primary outcomes due to the absence of missing data. $P<0.05$ was considered statistically significant.

Ethical considerations

Ethical approval for this study was obtained from the Ethics Committee of the Basra Health Directorate). All procedures were conducted in accordance with the ethical standards of the committee and the principles of the Declaration of Helsinki. Prior to recruitment, the study protocol, including objectives, methods, and data collection procedures was reviewed and approved by the scientific and ethical review board at the College of Pharmacy, University of Basrah. Written informed consent was obtained in a confidential setting before enrollment, and participants were informed of their right to withdraw without repercussions for their clinical care. Safety measures included screening for hepatic or gastrointestinal risk, counseling regarding potential adverse effects of nimesulide, and monitoring for intolerance or complications throughout participation.

3. Results

As shown in Table 1, in the metformin group, androgenic indices declined meaningfully over three weeks. Both total and free testosterone decreased with large t statistics and highly significant P-values, supporting a biochemical improvement in hyperandrogenism. LH also fell substantially, while FSH rose modestly yet significantly, indicating a more favorable pituitary-ovarian signal. DHEA-S showed a small but significant reduction, suggesting a modest adrenal contribution to overall androgen lowering. Collectively, these paired changes indicate that metformin monotherapy improved the hormonal milieu, with the most pronounced effects observed for serum testosterone fractions and LH, consistent with partial normalization of gonadotropin dynamics over the short treatment interval.

The results of Table 2 showed that adjunctive nimesulide produced marked within-group hormonal improvements beyond metformin's baseline effects. Total testosterone fell by ~0.38 ng/mL with an extremely large effect size, and free testosterone decreased significantly, indicating robust attenuation of biochemical hyperandrogenism. LH declined substantially, whereas FSH increased, consistent with a shift toward more physiological pituitary signaling. DHEA-S decreased modestly, hinting at a smaller but measurable adrenal component. The magnitude of change particularly for total testosterone and LH was large, suggesting clinically meaningful effects over a short exposure. These findings support anti-inflammatory co-treatment as a plausible strategy to enhance endocrine rebalancing in women with PCOS.

Table 1. Hormonal markers pre- vs post-treatment in Metformin group

Variable	Pre-treatment Mean±SD	Post-treatment Mean±SD	t-statistic	df	P-value
LH (IU/L)	10.85±1.36	7.03±1.65	23.09	49	<0.0001
FSH (IU/L)	4.36±2.24	4.58±2.26	-2.64	49	0.011
DHEA-S (µg/dL)	384.30±157.26	370.22±152.01	2.60	49	0.012
Free Testosterone (pg/mL)	8.29±0.85	6.42±1.29	10.67	49	<0.0001
Total Testosterone (ng/mL)	0.98±0.23	0.63±0.15	11.56	49	<0.0001

Paired t-test comparing within-group pre/post values; Negative t indicates post>pre.

Table 2. Hormonal markers pre- vs post-treatment (after 3 weeks of treatment) in Nimesulide+ Metformin group

Variable	Pre-treatment Mean ± SD	Post-treatmentMean ± SD	Mean Diff	95% CI (Lower–Upper)	t-value	df	P-value	Cohen's d
LH (mIU/mL)	11.32±2.29	6.83±2.29	4.49	3.89-5.09	14.960	49	<0.001	2.137
FSH (mIU/mL)	4.74±2.48	6.00±2.32	-1.26	-1.57- -0.95	-8.080	49	<0.001	-1.154
DHEA-S (µg/dL)	368.66±168.75	342.70±153.72	25.96	12.85-39.08	3.981	49	<0.001	0.569
Free Testosterone (pg/mL)	7.93±2.09	6.81±2.69	1.11	0.50-1.73	3.664	49	0.001	0.523
Total Testosterone (ng/mL)	0.949±0.178	0.565±0.157	0.384	0.343-0.425	18.733	49	<0.001	2.676

Mean differences are Pre-Post (negative values indicate an increase). Effect size = Cohen's d.

As presented in Table 3, at post-treatment, the combination group exhibited significantly higher FSH than metformin alone, consistent with the paired results showing a within-group rise in FSH under adjunctive therapy. Post-treatment LH, DHEA-S, and free testosterone did not differ significantly between the two groups, likely reflecting overlapping dispersion and the study's short exposure period. The pattern

implies that the clearest between-group signal was an FSH elevation with combination therapy, while androgens trended lower within both groups. These results suggest that although both regimens improved hyperandrogenism, adjunctive nimesulide may have exerted additional effects on gonadotropin dynamics rather than producing large between-group separations in androgen levels at three weeks.

The model for FSH-post was statistically significant, explaining ~21% of variance. Group assignment independently predicted higher FSH after treatment, aligning with the between-group comparison and suggesting a treatment-related effect of adjunctive nimesulide on pituitary output. CRP-post was also positively associated with FSH-post, though this manuscript centers on hormones rather than inflammatory endpoints. Other hormonal predictors including LH-post, DHEAS-post, and free testosterone did not reach significance, with DHEAS-post showing only a trend. Overall, the analysis indicates that treatment allocation was the dominant determinant of post-treatment FSH variability, while concurrent hormonal measures contributed minimally within this multivariable framework (Table 4).

Although the overall regression did not meet significance, two predictors showed significant associations with post-treatment free testosterone. Higher cholesterol related to lower free testosterone, whereas higher IL-6 related to higher free testosterone, indicating potential interplay between lipid/inflammatory status and androgen bioavailability. Treatment group was not a significant independent predictor after adjustment, and classic gonadotropins (LH, FSH) were also non-significant. The modest R^2 implies that additional unmeasured factors likely influence free testosterone after short-term therapy. Nonetheless, the directions of association are consistent with mechanisms linking systemic milieu to androgen transport and synthesis in PCOS (Table 5).

Table 3. Post-treatment hormonal parameters between the two groups of the study

Parameter	Metformin Mean±SD (n=50)	Combo Mean±SD (n=50)	Mean Diff	t	Df	P (2-tailed)
LH-post (mIU/mL)	7.03±1.65	6.83±2.29	0.20	0.486	98	0.628
FSH-post (mIU/mL)	4.58±2.26	6.00±2.32	-1.41	-3.054	98	0.003
DHEAS-post (µg/dL)	370.22±152.01	342.70±153.72	27.52	0.891	98	0.375
Free-Tes-post (pg/mL)	6.42±1.29	6.81±2.69	-0.39	-0.913	98	0.364

Independent samples t-test; variances assessed by Levene's test; Bold p indicates significance in the source.

Table 4. Multiple linear regression predicting post-treatment FSH

Predictor	B	Std. Error	Beta	T	P
(Constant)	-2.116	3.214	—	-0.658	0.512
LH-post	0.029	0.123	0.024	0.236	0.814
DHEAS-post	0.003	0.002	0.176	1.748	0.084
TG-post	-0.005	0.008	-0.063	-0.629	0.531
HDL-post	-0.018	0.036	-0.051	-0.504	0.616
Cholesterl-post	0.000	0.002	0.026	0.193	0.847
Free-Tes-post	0.171	0.115	0.151	1.483	0.142
IL6-post	-0.228	0.289	-0.107	-0.789	0.432
CRP-post	0.725	0.294	0.286	2.467	0.016
Group	2.145	0.576	0.451	3.726	<0.001

Model: R=0.454, R^2=0.206, Adj R^2=0.125; Std. Error=2.235; ANOVA F (9,88)=2.543, P=0.012. Dependent variable FSH-post; all predictors entered simultaneously.

The multivariable model for DHEA-S did not achieve statistical significance, with predictors collectively explaining ~11% of variance. None of the hormonal predictors LH-post, FSH-post, or free testosterone were significant, although triglycerides and IL-6 trended toward association. From a hormone-

centric perspective, these results suggest that short-term post-treatment adrenal androgen levels were relatively uncoupled from contemporaneous gonadotropins and circulating free testosterone in this dataset.

Table 5. Multiple linear regression predicting post-treatment free testosterone

Predictor	B	Std. Error	Beta	T	p
(Constant)	3.914	2.910	—	1.345	0.182
Group	0.730	0.560	0.174	1.305	0.195
LH-post	0.001	0.112	0.001	0.009	0.993
FSH-post	0.142	0.096	0.161	1.483	0.142
DHEAS-post	0.001	0.001	0.062	0.585	0.560
TG-post	-0.009	0.007	-0.139	-1.350	0.180
HDL-post	-0.002	0.033	-0.007	-0.066	0.948
Cholesterol-post	-0.003	0.001	-0.337	-2.554	0.012
IL6-post	0.672	0.255	0.359	2.641	0.010
CRP-post	0.073	0.277	0.033	0.263	0.793

MD ependent variable Free-Tes-post; significance defined as P<0.05 in source.

Table 6. Multiple linear regression predicting post-treatment DHEA-S

Predictor	B	Std. Error	Beta	T	p
(Constant)	259.763	192.637	—	1.348	0.181
LH-post	-7.502	8.199	-0.098	-0.915	0.363
FSH-post	8.085	6.606	0.126	1.224	0.224
TG-post	0.858	0.492	0.178	1.744	0.085
HDL-post	-2.572	2.414	-0.112	-1.065	0.290
Cholesterol-post	-0.068	0.099	-0.093	-0.684	0.496
Free-Tes-post	2.849	7.777	0.039	0.366	0.715
IL6-post	31.132	18.855	0.229	1.651	0.102
CRP-post	-9.130	17.086	-0.056	-0.534	0.594

Model: R=0.334, R^2=0.112, Adj R^2=0.032; Std. Error=150.244; F=1.401, P=0.207. Dependent variable DHEAS-post; α=0.05; n=98.

4. Discussion

The results of the present study demonstrated a statistically and clinically significant improvement in androgenic and gonadotropic profiles following a three-week course of metformin monotherapy in PCOS women. Metformin improved hormonal and metabolic profiles in women with PCOS **(15)**. Notably, in the present study, both total and free testosterone levels were significantly reduced, suggesting a potent effect of metformin on hyperandrogenism, a hallmark of PCOS. Luteinizing Hormone (LH) showed a substantial decline, while Follicle-Stimulating Hormone (FSH) increased slightly but significantly, indicating a potential normalization of pituitary-ovarian signaling. Additionally, the small yet significant drop in Dehydroepiandrosterone Sulfate (DHEA-S) points to a modest reduction in adrenal androgen output. These collective hormonal shifts suggest that metformin monotherapy can improve the endocrine landscape in women with PCOS over a relatively short duration.

These findings are consistent with a number of recent studies. A large randomized controlled trial by Andræ et al., (2020) found that metformin reduced total testosterone and androstenedione in non-obese women with PCOS, particularly when carrying a male fetus **(16)**, which supports the current study's observation of reduced androgenic markers. Similarly, Pradas et al., (2019) confirmed decreased androgenic metabolites and beneficial changes in markers of lipid and oxidative stress after 12 weeks of metformin treatment **(17)**, which matches the current results of hormone improvement. Moreover, Ohara et al., (2021) reported that metformin reduces androgen receptor expression and improves endometrial receptivity by upregulation of HOXA10 and acts to counteract androgen-driven pathology **(18)**.

Attia et al., (2023) had also identified a decrease in serum androgen and improvement in frequency and regularity of menstruation in Saudi women with PCOS treated with metformin, supporting the benefits of metformin on hormones (ref), as reported in the current study **(20)**. Provided further support by identifying hyperandrogenism and menstrual irregularity as strong predictors of response to metformin therapy, echoing its effectiveness in improving biochemical hyperandrogenism **(20)**.

However, a review studt by Saadati and Mason (2025) argued that while metformin improves insulin resistance and menstrual regularity, it may not consistently alleviate clinical hyperandrogenic features such as hirsutism and acne, particularly when used as monotherapy **(21)**. Similarly, a study by Løvvik et al., (2016) reported no significant reduction in androgen levels during pregnancy despite metformin use, suggesting that its androgen-lowering effects might be context-specific or vary with physiological states such as gestation.

The current study's findings indicated that metformin monotherapy significantly improves serum testosterone levels, LH, and FSH in women with PCOS are largely supported by recent literature, though some conflicting results in different clinical contexts highlight the need for individualized treatment strategies and longer follow-up studies.

In the present study, the nimesulide+metformin group revealed substantial reductions in Luteinizing Hormone (LH), free testosterone, and total testosterone, all with large effect sizes (Cohen's d ranging from 0.52 to 2.68). Follicle-Stimulating Hormone (FSH) increased significantly, while DHEA-S decreased modestly but significantly. The combination of lower androgen levels and more physiological gonadotropin profiles suggests that nimesulide might enhance metformin's endocrine effects via anti-inflammatory mechanisms. Clinically, this could translate to improved ovulatory function and reduced hyperandrogenic symptoms in PCOS patients.

Comparing these findings with other recent studies yields both supportive and contrasting results. In a 2025 study, Kumar et al., reported that women with PCOS had elevated levels of both classical (testosterone, DHEAS) and novel androgens (11-ketotestosterone, DHT), showing a strong positive correlation between these markers. However, the study did not assess any pharmacologic intervention like nimesulide, so it does not directly contradict the present findings but reinforces the role of these androgens in PCOS pathophysiology **(23)**.

In contrast, a recent prospective trial by Abdelazim et al., (2020) found that both total and free testosterone levels, along with androstenedione, were significantly elevated in PCOS patients versus controls. Interestingly, DHEA-S levels were not elevated or deemed diagnostically useful in this cohort, a finding that supports the current study's observation of modest DHEA-S changes after intervention. This suggests that while testosterone is a reliable androgenic marker for PCOS, adrenal contributions like DHEA-S may be more variable **(24)**.

Zakareya et al., (2020) evaluated the impact of laparoscopic ovarian drilling on PCOS hormonal profiles and found significant reductions in total and free testosterone, LH, and DHEA-S after the procedure, with FSH remained stable. Their findings align with the present study in terms of hormonal directionality but diverge in that FSH did not rise in their cohort. This difference could reflect the contrasting mechanisms of a surgical versus pharmacological intervention **(25)**.

In addition, the study by Szczuko et al., (2016) emphasized that inflammatory cytokines like TNF-α negatively correlated with DHEA-S in hyperandrogenic women, suggesting an interaction between inflammation and adrenal steroid pathways **(26)**. This mechanistic insight complements the present

study's rationale for using nimesulide, an anti-inflammatory drug, to modulate hormonal imbalances. The observed reductions in DHEA-S and testosterone support this hypothesis, although the present study did not directly assess TNF-α levels.

The current study's findings align with recent evidence that androgen levels especially testosterone are modifiable in PCOS with both pharmacologic and surgical interventions. The rise in FSH and the robust reduction in LH and testosterone reinforce the utility of adjunctive anti-inflammatory treatment. However, heterogeneity in DHEA-S findings across studies suggests this adrenal androgen may be less responsive or variable depending on the intervention type and population.

The findings of the current study revealed a statistically significant increase in FSH levels in the combination group, while LH, DHEAS, and free testosterone levels showed no significant between-group differences. This suggests a unique modulatory effect of the adjunctive therapy on gonadotropins, particularly FSH, possibly reflecting central feedback changes or altered follicular signaling. The absence of significant reductions in androgen markers between groups could be due to the short treatment duration of three weeks. This finding aligns partially with Krysiak et al., (2023), who demonstrated that metformin alone reduced LH, LH/FSH ratio, and testosterone in women with PCOS, suggesting metformin's ability to suppress gonadotropin and androgen excess through insulin-sensitizing and central neuroendocrine effects **(27)**. However, they did not evaluate the use of adjunct anti-inflammatory agents like nimesulide, making the FSH-specific enhancement in the present study noteworthy. In contrast, the study by Coşar et al., (2024) utilizing a PCOS rat model showed that metformin and antioxidant glutathione both significantly reduced serum testosterone and improved follicle morphology, suggesting androgen suppression may be more prominent with longer intervention periods or additional anti-inflammatory or antioxidant support (ref). Similarly, Xue et al., (2019) found in a mouse model that both metformin and inulin significantly decreased testosterone and inflammatory cytokines (e.g., IL-6, IL-17A), indicating that anti-inflammatory pathways might modulate androgen biosynthesis and systemic inflammation, contributing to PCOS pathophysiology **(29)**.

Interestingly, the synergistic use of Ceratonia siliqua seed oil with metformin in a recent rat study showed enhanced effects on FSH, LH, and testosterone via PI3K/AKT signaling, further supporting the idea that adjunct agents may modulate hypothalamic-pituitary-ovarian axis differently, particularly in boosting gonadotropin levels **(30)**.

In contrast to the current study, a study by Kurbat and Swadi (2024) reported that the combination of myoinositol and metformin led to a greater reduction in inflammatory cytokines (hs-CRP and IL-18), which are often associated with hyperandrogenism in PCOS. This may imply that the anti-inflammatory profile of the adjunct therapy in the present study did not exert a sufficient effect within the limited duration to cause measurable androgen suppression **(31)**. Further, Enache et al., (2023) explored the pharmacokinetic interaction of nimesulide with various delivery agents and suggested that micellar systems could enhance drug bioavailability. Although not specific to hormonal parameters, such pharmacokinetic modulation may be relevant in optimizing anti-inflammatory impact on hormonal pathways in PCOS **(32)**.

The current study also stands in contrast with the study by Catarro et al., (2019), who highlighted that COX-2 inhibitors like nimesulide exhibit anti-inflammatory and even antitumor properties, potentially reducing prostaglandin-mediated stimulation of androgen production **(33)**. Their findings support a theoretical foundation for anti-inflammatory adjuncts reducing androgen markers, yet this was not significantly observed in the current trial, possibly due to its short-term design.

Collectively, while the present study demonstrates a statistically significant increase in FSH following combination therapy and trends toward androgen reduction, the lack of significant between-group differences in LH, DHEAS, and free testosterone suggests a limited impact of adjunctive nimesulide on short-term androgen dynamics. This could reflect insufficient treatment duration, suboptimal dosing of the anti-inflammatory agent, or the possibility that nimesulide's modulatory effects are more prominent at the level of central gonadotropin release rather than ovarian androgen synthesis. There is a growing body of evidence supporting the synergistic potential of anti-inflammatory or antioxidant agents with metformin in PCOS treatment, though the hormonal endpoints achieved vary significantly depending on study design, duration, and model system.

5. Conclusion

As evidenced by the results of the present study, in women with PCOS, three weeks of metformin produced significant reductions in total and free testosterone alongside favorable gonadotropin shifts. Adding nimesulide preserved these benefits and yielded larger within-group declines particularly for total testosterone and LH while producing a clear between-group signal of higher post-treatment FSH. Multivariable analysis indicated that treatment allocation independently predicted FSH after therapy, whereas free testosterone tracked inversely with total cholesterol and positively with IL-6; adrenal androgen responses (DHEA-S) were modest and not well explained by contemporaneous hormones or lipids. Collectively, the data supports the biological plausibility of short-course anti-inflammatory co-treatment to enhance endocrine rebalancing. Given the non-randomized design, short exposure, and limited

between-group separation for androgens at follow-up, confirmatory randomized studies with longer duration and clinical endpoints (ovulation, mFG score, acne) are warranted.

6. Declarations

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Ethical Considerations

Ethical approval for this study was obtained from the Ethics Committee of the Basra Health Directorate (202102). All procedures were conducted in accordance with the Declaration of Helsinki and relevant national guidelines. Written informed consent was obtained from all participants prior to enrollment in the study. Participants' confidentiality and anonymity were strictly maintained throughout the study.

Authors' Contributions

Reyam Alsaadi was responsible for the study design, data collection, statistical analysis, interpretation of results, and manuscript preparation.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this research.

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