



RESEARCH ARTICLE

Metformin Modulated Conventional and Biochemical Markers in Polycystic Ovarian Women

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ARTICLE INFO	ABSTRACT
Received: Apr 24, 2024 Accepted: June 13, 2024	<p>Polycystic ovary syndrome (PCOS) is the most common form of chronic female disease associated with androgen excess. The purpose of this study is to evaluate the serum level of Anti-Mullerian Hormone (AMH), 17-hydroxyprogesterone (17-OHP), and Dehydroepiandrosterone sulfate (DHEAS) in women with PCOS and to investigate the effect of metformin on AMH, 17-OHP, and DHEAS. Methods: A total of 261 subjects (141 PCOS and 120 control) were enrolled in the present study. The body mass index is determined before and after therapy. They take metformin 850 mg twice daily for three months and provide fasting blood samples on the second day of menstruation before and after treatment. Hormones quantified before and after metformin therapy. The DHEAS level was significantly higher in PCOS cases compared to controls. After metformin intake, those patients exhibit non-significant differences in DHEAS after metformin treatment. Serum levels of TSH in women with PCOS were significantly elevated compared to the healthy control group. However, the study found no significant difference ($p>0.05$) in TSH levels in the treated group with metformin compared with pre-treatment. Metformin decreased AMH and 17OHP levels without affecting DHEAS levels in patients with PCOS.</p>
<p>Keywords</p> <p>Metformin Polycystic ovarian syndrome Anti-mullerian hormone Hydroxyprogesterone Dehydroepiandrosterone</p>	
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INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a chronic anovulation in women without specific underlying diseases of the adrenal or pituitary glands (Sachdeva et al., 2019; Jam et al., 2018). PCOS is a common endocrine disorder affecting 4–20% of reproductive-aged women (Deswal et al., 2020; Wardat et al., 2024). PCOS is characterized clinically by hirsutism, acne, and androgen-dependent alopecia and biochemically by elevated serum concentrations of androgens, particularly testosterone and androstenedione (Iliodromiti et al., 2014; Zakariya et al., 2023). Obesity is common but not universal (Kakoly et al., 2019; Tashtoush et al., 2023b). Typically, these features are associated with hypersecretion of luteinizing hormone and androgens but with normal or low serum concentrations of follicle-stimulating hormone (Chun, 2014; Jam et al., 2014). The early descriptions of the syndrome were based on ovarian morphology this has not been considered an essential requirement for the diagnosis. The recent application of modern, high-resolution diagnostic ultrasonography has again tipped the balance toward a more morphologically insulin resistance, chronic anovulation and hyperandrogenism, androgen excess, hirsutism, acne, PCOS has been linked to obesity, type II diabetes mellitus (TII DM) dyslipidemia heart disease and hypertension, and endocrine abnormalities may include increased syndrome free testosterone levels, low sex hormone binding globulin, and high luteinizing hormone/follicle-stimulating hormone may develop with many other

related endocrine and metabolic diseases, and have increased risk of suffering endometrial cancer, impaired glucose tolerance, diabetes, and cardiovascular disease researches about the pathogenesis of PCOS mainly focus on two interrelated metabolic elements-insulin resistance (IR) and hyperandrogenism nevertheless, pathogenesis of PCOS remains unclear (Caglar et al., 2013; Jarrah et al., 2022b).

Metformin is a biguanide-class oral synthetic antidiabetic drug, the most commonly used treatment to increase insulin sensitivity in insulin-resistant (IR) conditions such as diabetes, prediabetes, PCOS, and obesity. The mechanisms of metformin action have remained obscure, despite multiple pathways of action being proposed, including a decrease of hepatic glucose production, an increase of peripheral glucose disposal, a reduction of intestinal glucose absorption, inhibiting mitochondrial respiration and gluconeogenesis, activating adenosine monophosphate-activated protein kinase (AMPK), increasing insulin sensitivity, antagonizing the effects of glucagon, and increasing fatty acid oxidation (Khalaf et al., 2024; Alneyadi et al., 2023b).

17-Hydroxyprogesterone (17 α -OHP, Figure 1) is an agonist of the progesterone receptor (PR) similar to progesterone, albeit weakly in comparison. In addition, it is an antagonist of the mineralocorticoid receptor (MR) as well as a partial agonist of the glucocorticoid receptor (GR), albeit with very low potency at the latter site, also similar to progesterone (Stogowska et al., 2022; Tashtoush et al., 2023a). 17 α -OHP is derived from progesterone via 17 α -hydroxylase (encoded by CYP17A1). 17 α -OHP increases in the third trimester of pregnancy primarily due to fetal adrenal production. This steroid is primarily produced in the adrenal glands and to some degree in the gonads, specifically the corpus luteum of the ovary. Dehydroepiandrosterone sulfate (DHEA sulfate or DHEA-S, Figure 1) also known as androstenedione sulfate, is an endogenous androstane steroid that is produced by the adrenal cortex. It is the 3 β -sulfate ester and metabolite of dehydro-epiandrosterone and circulates in far greater relative concentrations than DHEA (Boucher et al., 2024). The steroid is hormonally inert and is instead an important neurosteroid and neurotrophin. This study aimed to study the effects of metformin therapy on serum anti-mullerian hormone (AMH, Figure 1), 17-hydroxyprogesterone (17OHP), and dehydroepiandrosterone sulfate (DHEAS) levels in women with polycystic ovarian syndrome.

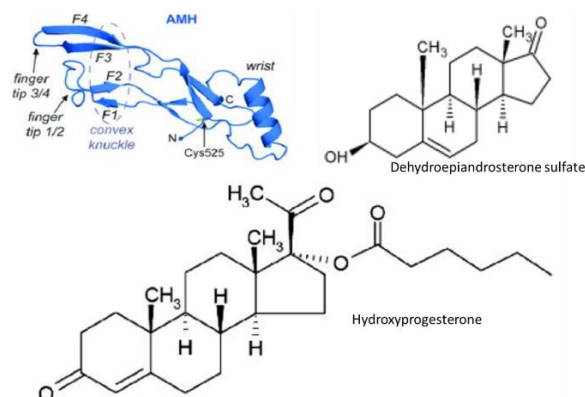


Figure 1. Structure of AMH(Hart et al., 2021), 17 α -OHP (Chollet and Jozwiakowski, 2012; Alneyadi et al., 2023a), and DHEAS(Zhang et al., 2015; Kanval et al., 2024).

MATERIALS AND METHODS

Study design: This cross-sectional study, was used for the investigation of some biochemical markers in patients with PCOS before and after metformin treatment.

Study population: The present study was conducted at Kirkuk General Hospital and Azadi General Hospital from March 2023 to January 2024. One hundred forty-one patients newly diagnosed PCOS women, complete the follow-up study and agree to continue on metformin treatment for three months, the duration of the follow-up. In addition, a group of 120 healthy women without PCOS matching in the mean age and BMI to the PCOS women were also recruited in the study as a control group and their ages between 16-40 years old. The diagnosis of PCOS was made according to the Rotterdam criteria. Specifically, patients with an ovulation and clinical and/or biochemical hyperandrogenism were enrolled. After they visit the gynecologist physicians and are diagnosed according to their symptoms and signs and the picture of ovarian ultrasound, their weight and height are measured and other related information such as age, duration of infertility, and number of children.

Treatment: All patients received metformin (Glucophage) at a dosage of 850 mg daily for 3 months. In addition, standard clinical evaluations and laboratory analyses were performed at baseline and after 3 months of treatment as safety measures. After the treatment period, in each patient, all of the above parameters were reevaluated as at baseline.

Inclusion criteria: Women newly diagnosed with PCOS according to modified Rotterdam criteria which include; the presence of clinical and/or biochemical signs of hyperandrogenism alongside one of the following: oligo- or anovulation and/or polycystic ovaries, depending on ultrasound examination, clinical features and laboratory hormonal tests by a specialist gynaecologist.

Exclusion Criteria of Women with PCOS: Women who had diabetes mellitus, hyperprolactinemia, congenital adrenal hyperplasia, thyroid disorders, Cushing syndrome, androgen-secreting tumours, hypertension, and smoking. Women had been treated with any hormone and confounding medications, including oral contraceptive agents, antilipidemic drugs, and insulin-sensitizing drugs that might affect the ovarian function and /or metabolic criteria; within 3 months before enrollment.

Biochemical parameters: Detection of measured parameters including AMH, AMH, 17-OHP, and DHEAS (Biomerieux SA Etoile-France) using COBAS as per manufacturer instruction.

Statistical Analysis: Data are expressed as the means \pm SD. Statistical analyses were performed using Student's t-test or one-way analysis of the variance (ANOVA). All the data were analyzed by T-test, and data were considered to be statistically significant at P values < 0.01 and < 0.05 . All data were analyzed using SPSS (version 20).

RESULTS

The data analysis of hormonal levels in PCOS versus a control group underscores significant biochemical discrepancies, which potentially illuminate underlying pathogenic mechanisms. Specifically, the AMH, 17OHP, and DHEAS were markedly elevated in the PCOS cohort compared to their healthy counterparts. Quantitatively, AMH levels in the PCOS group soared to 5.79 ± 1.95 , markedly higher than the 1.76 ± 1.87 observed in the control group—a statistically significant difference with a p-value ≤ 0.05 . Similarly, 17OHP exhibited an escalation from 1423.56 ± 82.63 in controls to 6131.02 ± 154.16 in those with PCOS, further demonstrating profound deviations linked to this endocrine disorder. Additionally, DHEAS levels were significantly heightened at 211.63 ± 24.72 in the PCOS population compared to just 89.47 ± 14.98 among controls, reinforcing these findings' statistical robustness ($p \leq 0.05$). These elevations highlight an altered steroidogenesis pathway integral to PCOS pathophysiology and point towards potential biomarkers for diagnosis and therapeutic targets within affected individuals. (Table 1).

Table 1. Evaluation of AMH, 17OHP, and DHEAS mean levels of PCOs and control groups

Parameters	PCOs	Control	P. Value
AMH (ng/ml)	5.79±1.95	1.76±0.87	0.001
17OHP(pg/mL)	6131.02±154.16	1423.56±82.63	0.0001
DHEA-S(μmol/L)	211.63±24.72	89.47±14.98	0.005

This study reveals critical insights into the biochemical impacts of metformin treatment on patients with PCOS, specifically noting significant decreases in AMH and 17OHP levels. The findings suggest that after metformin administration, there is a notable reduction in AMH and 17OHP concentrations, with P-values less than 0.05 indicating statistical significance however, the study also highlights that metformin does not affect DHEAS levels, a crucial androgenic hormone often elevated in PCOS cases which can contribute to hirsutism and other hyperandrogenic manifestations. This differential hormonal response underscores the specificity of metformin's mechanism of action and suggests that while it effectively targets certain endocrine pathways disrupted in PCOS, it does not universally mitigate all hormonal abnormalities associated with the condition. Therefore, this evidence positions metformin as a targeted therapeutic agent within a broader management plan for PCOS, necessitating complementary treatments to address hyperandrogenism more comprehensively.

Table 2. Assessment of measured parameters in PCOS patients pre and post-Metformin therapy

Parameters	Pre-metformin	Post- metformin	P. Value
AMH(ng/ml)	5.79±1.95	4.89±1.60	0.015
17OHP(pg/mL)	6131.02±5416.78	5128.28±143.078	0.069
DHEAs(μmol/L)	211.63±24.72	204.95±22.97	0.656

The study conducted on the levels of AMH and 17OHP in diabetic and non-diabetic patients within the PCOS group demonstrated a lack of significant differences between these cohorts. Specifically, AMH levels were similar in both diabetic (6.18±1.89 ng/ml) and non-diabetic patients (5.46±1.97 ng/ml), showing no statistical significance with a p-value greater than 0.05. This trend continued with measurements of 17OHP; diabetic patients exhibited mean levels of 6476.76±160.58 pg/mL compared to non-diabetic patients' levels of 5840.60±155.37 pg/mL, also resulting in an insignificant difference as evidenced by the same p-value threshold exceeding 0.05. Furthermore, another subset analysis indicated that the mean ± SD level of 17OHP was similarly statistically indifferent between diabetic patients at 216.56±27.98 pg/mL and their non-diabetic counterparts at 205.76±25.74 pg/mL, reaffirming that diabetes does not significantly impact these hormone levels within the PCOS patient group according to this study's findings (P>0.05). These results suggest that while metabolic syndrome complicates PCOS management, it might not differentially alter certain endocrine parameters like AMH and 17OHP across diabetic statuses in PCOS sufferers, emphasizing the need for broader perspectives in future research initiatives targeting hormonal profiles within this demographic (Table 3).

Table 3. Evaluation of measured parameters in diabetic versus non-diabetic PCOS patients

Parameters	Diabetic	Non-Diabetic	P. Value
AMH(ng/ml)	6.18±1.89	5.46±1.97	0.214
17OHP(pg/mL)	6476.76±160.58	5840.60±155.37	0.696
DHEAs(μmol/L)	216.56±27.98	205.76±25.74	0.885

The present study indicates that there are no significant differences in the levels of Dehydroepiandrosterone sulfate (DHEAS), 17OHP, and AMH between hypertensive and non-

hypertensive patients within the PCOS group. Specifically, the DHEAS levels were found to be statistically similar in both hypertensive and non-hypertensive PCOS patients, with mean values of 249.0 ± 30.367 $\mu\text{g/dL}$ versus 237.21 ± 29.33 $\mu\text{g/dL}$ respectively, showing a P-value greater than 0.05, indicating no significant difference. Similarly, for 17OHP levels, there was also no significant difference observed between the two groups, with mean values of 6221.94 ± 5300.71 ng/dL in hypertensive patients compared to 5803.70 ± 6106 ng/dL in their non-hypertensive counterparts ($P > 0.05$). Furthermore, AMH levels did not significantly differ between hypertensive and non-hypertensive PCOS patients either, with mean values of 5.99 ± 2.11 ng/mL and 5.73 ± 1.93 ng/mL , respectively ($P > 0.05$) (Table 4).

Table 4. Evaluation of measured parameters in hypertensive versus non-hypertensive PCOS patients

Parameters	Hypertensive	Non-hypertensive	P. Value
AMH(ng/ml)	5.99 ± 1.01	5.73 ± 1.13	0.719
17OHP(pg/mL)	6221.94 ± 5300.71	5803.70 ± 6106	0.832
DHEAs($\mu\text{mol/L}$)	249.0 ± 30.367	237.21 ± 29.33	0.595

DISCUSSION

Metformin, a commonly prescribed medication for managing PCOS, has demonstrated notable efficacy in modulating hormone levels that are often disrupted in this condition. Specifically, research indicates that metformin significantly reduces serum levels of AMH and 17OHP without causing appreciable changes in DHEAS concentrations among PCOS patients. Elevated AMH levels in PCOS are typically reflective of the increased number of antral follicles, contributing to the pathophysiology of the syndrome by exacerbating ovarian dysfunction and anovulation. By decreasing AMH, metformin potentially enhances follicular maturation and regularizes menstrual cycles. Similarly, high levels of 17OHP—a marker for adrenal hyperandrogenism—are indicative of excessive androgen production that can manifest as hirsutism and acne in PCOS sufferers. Metformin's ability to lower 17OHP suggests its role in attenuating these hyperandrogenic symptoms. However, the unaltered DHEAS level points to a selective influence on specific androgen pathways rather than a broad-spectrum suppression of all androgenic activity. This specificity underscores the nuanced impact of metformin on hormonal regulation within PCOS pathology, making it a valuable therapeutic agent for targeted symptom management while minimizing potential side effects related to broader hormonal alterations.

This study elucidates a significant elevation of AMH levels in women with PCOS compared to the control group, aligning with findings by Jihad and Sarhat (2023), who observed substantially higher serum AMH levels in PCOS patients than in controls ($p < .001$). Correlation analysis revealed that AMH levels positively correlated with luteinizing hormone (LH) and total cholesterol content but showed no correlation with insulin resistance parameters, as noted by Lin et al. (2011). To investigate whether metformin treatment affects AMH levels in PCOS patients, we reviewed studies evaluating serum AMH before and after metformin therapy. The data indicated that metformin exerts a potent inhibitory effect on AMH levels, underscoring its utility beyond alleviating insulin resistance; it is also efficacious in restoring menstrual cycles and inducing ovulation. Supporting this, Zhou et al. (2023), found decreased AMH levels post-metformin treatment. Although Foroozandard et al. (2017), study was pioneering in demonstrating metformin's capacity to lower AMH in PCOS patients, subsequently, (Tomova et al. (2011), research indicated that those who resumed regular menstrual cycles post-treatment exhibited a 16.27% decrease in AMH levels. A meta-analysis corroborated these findings by showing a substantial reduction in circulating AMH following metformin therapy, suggesting an improvement of polycystic ovarian morphology—a result echoed by (Yin et al., 2022). Notably, metformin's efficacy appears limited when baseline AMH levels are below 4.7 ng/ml ; thus,

implying it does not jeopardize ovarian function at these physiological ranges indicative of ovarian reserve (Lupoli et al., 2014). These insights affirm the multi-faceted benefits of metformin for PCOS management while highlighting nuances related to baseline AMH variability and therapeutic outcomes.

The present study elucidates the elevated levels of 17-OHP among women with PCOS as compared to a control group, corroborating findings by Stogowska et al. (2022). It is well-documented that women with PCOS exhibit statistically higher baseline concentrations of 17-OHP, which can be attributed to anovulation and subsequent low serum progesterone levels. Occasional ovulation in these individuals results in luteal phase progesterone levels akin to those observed in non-PCOS women. Notably, research indicates that among the various progestins, 17-OHP levels are significantly elevated in PCOS due to its production by theca cells, where it functions as an androgen precursor. Further supporting this observation, Dunaif et al. (2008), demonstrated that 17-OHP responses to gonadotropin stimulation effectively differentiate PCOS patients from normal controls in provocative studies on androgen production. Therefore, multiple studies concur on the increased serum concentration of 17-OHP being a distinguishing marker for PCOS (14, 15) (Dunaif et al., 2008; Stogowska et al., 2022). This biomarker not only underscores pathophysiological distinctions between PCOS and normal reproductive physiology but also suggests its potential utility in diagnostic evaluations and therapeutic monitoring for affected individuals.

Serum concentrations of 17-OHP and DHEA-S are elevated in women with PCOS, potentially due to glycemic control imbalances (Stogowska et al., 2022). Metformin administration at various therapeutic doses results in statistically significant reductions in 17-OHP levels and an increased pregnancy rate when compared to placebo. However, it is important to recognize that metformin is not primarily a fertility drug like clomiphene citrate (CC); rather, it indirectly induces ovulation by reducing insulin levels and is generally less effective than CC, which directly inhibits negative feedback on the hypothalamic-pituitary-ovarian (HPO) axis to induce ovulation (Begawy et al., 2010). Nonetheless, using metformin as adjunct therapy with CC significantly improves both ovulation rates and pregnancy outcomes. Beyond reproductive health, PCOS and obesity independently impact vascular endothelial function, yet the link between hyperinsulinemia and cardiovascular disease (CVD) remains independent of body weight. Women with PCOS frequently experience dyslipidemia, evidenced by low high-density lipoprotein (HDL) levels and elevated triglycerides—markers strongly predictive of CVD risk. Managing dyslipidemia is therefore essential for mitigating CVD risk in this population. Metformin has been shown to improve dyslipidemia by either directly affecting the hepatic metabolism of free fatty acids or indirectly enhancing insulin sensitivity through the reduction of hyperinsulinemia; however, it does not significantly impact total cholesterol levels. This observation aligns with findings from Abdalla et al. (2022) underscoring the nuanced role metformin plays in metabolic regulation within PCOS management strategies.

The study conducted by Boucher et al. (2024) elucidates the relationship between PCOS and elevated levels of DHEAS, revealing a substantial prevalence among women with PCOS and an intricate connection to insulin resistance. This hormonal disturbance is central to PCOS's defining characteristics: hyperandrogenism, chronic anovulation, infertility, and obesity. Borg et al. (2022) corroborate these findings in their prospective study involving 40 obese women with PCOS referred to a university hospital. The researchers assessed levels of DHEAS and fasting blood sugar (FBS) before administering metformin at 500 mg thrice daily for eight weeks. Their results demonstrated that while metformin therapy significantly reduced body mass index (BMI), menstrual cycle length, acne severity, and hirsutism scores—crucial clinical symptoms of PCOS—it did not markedly affect DHEAS levels. This aligns with earlier studies reporting no significant alteration in DHEA

concentrations post-treatment compared to pre-treatment phases in PCOS patients. As such, while the management of metabolic symptoms through agents like metformin proves beneficial in improving several aspects of this complex syndrome's phenotype, its impact on hormonal profiles like DHEAS remains limited. These insights reinforce the multifaceted nature of PCOS pathophysiology where insulin resistance intertwines with hyperandrogenemia but may require targeted therapeutic interventions beyond standard metabolic treatments for comprehensive management.

The present study diverges from the conclusions drawn by Verdiesen et al. (2021), who argue that PCOS is not the most common cause of hyperandrogenism and an ovulatory infertility in reproductive-aged women. Women with PCOS exhibit a broad spectrum of phenotypes, complicating precise diagnosis and grading; this polymorphic presentation suggests diverse underlying pathophysiologies that extend beyond reproductive dysfunction to lifelong health implications. Notably, women with PCOS are at heightened risk for cardiovascular diseases, type 2 diabetes mellitus (T2DM), dyslipidemia, atherosclerosis, and endometrial carcinoma (Wang et al., 2021). However, while the current evidence supports an association between AMH levels and androgen production as well as type 2 diabetes the mechanisms underlying these relationships remain unclear (Caglar et al., 2013). Moreover, although longitudinal analyses do not definitively establish differing AMH levels between women who develop T2DM compared to those who do not—perhaps due to underpowered study designs—the association between lower AMH levels and earlier menopause seems consistent across studies. This connection implies a potential link between ovarian ageing and increased T2DM risk independent of BMI (Chao et al., 2012; Iliodromiti et al., 2014). Our findings resonate with Ou et al. (2021), regarding the relationship between AMH levels and insulin resistance; among 681 patients studied, those with lower BMI and waist-to-hip ratios displayed higher mean antral follicle counts as AMH quartiles rose, without significant differences in blood pressure metrics or hypertensive status related to AMH levels. Similarly, Sachdeva et al. (2019) study indicates no substantial link between blood pressure and dehydroepiandrosterone sulfate, underscoring that cardiovascular disease risks may not be directly mediated by androgenic pathways (36). These insights collectively underscore the multifaceted nature of PCOS and its complex interactions with metabolic and endocrine systems throughout a woman's life span.

CONCLUSION

Metformin can decrease 17OHP levels in PCOS patients after three months of treatment. Metformin could not decrease or increase DHEAS levels in PCOS women after three months of treatment. Metformin after three months of treatment can decrease AMH levels in PCOS patients. There were no significant differences in the levels of AMH, 17OHP, and DHEAS in diabetic and non-diabetic patients of the PCOs group. No significant difference in AMH, 17OHP, and DHEAS was shown in hypertensive and non-hypertensive patients of the PCOs group.

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