Journal of Kerbala University, Vol. 22, Issue 4, December , 2025

Available at https://www.iasj.net/iasj

Iraqi Academic Scientific Journals

Journal homepage: https://journals.uokerbala.edu.iq/index.php/UOKJ

Research Article

Evaluating the impact of Metformin doses on Pituitary Hormones (FSH, LH, PRL, and Estrogen) regulation in women with PCOS

Doaa adil rabee

food science department/agriculture college/ University of Kerbala/ Kerbala/ Iraq

Article Info

Article history:

Received 6 -10-2025

Received in revised form 26-11-2025

Accepted 21-12-2025

Available online 31 -12 -2025

Keywords:

Metformin, Polycystic Ovary Syndrome (PCOS), Pituitary Hormone , Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH)

Abstract:

Objective: This study aimed to investigate how varying doses of metformin influence specific pituitary hormones (FSH, LH, PRL) and ovarian estrogen activity in women affected by polycystic ovary syndrome (PCOS). Estrogen was included because of its feedback regulation on pituitary gonadotropins within the hypothalamic–pituitary–ovarian axis.

Methods: Ninety women aged 16 to 45 years diagnosed with PCOS according to the Rotterdam criteria were randomly assigned to three treatment groups. Each group received a daily dose of metformin—500 mg, 800 mg, or 1000 mg—for a duration of three months. Post-treatment serum concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), and estrogen were measured using enzyme-linked immunosorbent assay (ELISA).

Results: Patients who received a daily dose of 1000 mg of metformin exhibited clear reductions in serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), indicating a measurable endocrine response to the higher dosage as well as to estrogen when compared with their initial baseline levels. Conversely, prolactin (PRL) levels showed a significant rise following treatment. This pattern of hormonal fluctuation appears to be linked to dosage intensity, suggesting a dose-dependent mechanism of endocrine modulation. These findings imply that progressive titration of metformin may exert regulatory effects on pituitary function in PCOS patients, thereby aiding in the restoration of hormonal equilibrium and enhancing reproductive outcomes.

Corresponding Author E-mail: doaa.a@uokerabala.edu.iq

Peer review under responsibility of Iraqi Academic Scientific Journal and University of Kerbala.

Introduction

Polycystic ovary syndrome (PCOS) is recognized as a common endocrine disorder affecting women during their reproductive years, and is marked by a broad spectrum of clinical features and etiological factors [1]. In contrast, ovarian cysts represent distinct anatomical entities. While most ovarian cysts are benign and asymptomatic, a small proportion may progress to malignancy, which highlights the necessity for early and accurate diagnostic distinction [2]. Proper classification of these cystic formations is essential for improving diagnostic reliability and informing appropriate therapeutic decisions. Although benign cysts are generally considered harmless, they may interfere with hormonal regulation and can result in pelvic pain or acute complications, including rupture or torsion. Therefore, timely clinical evaluation and personalized treatment planning are crucial to maintaining both reproductive and systemic health. [3]

Follicle-stimulating hormone (FSH) plays a central role in ovarian physiology, particularly in regulating gametogenesis and endocrine signaling. In females, FSH primarily targets granulosa cells, while in males, it acts on Sertoli cells. Recent investigations have expanded the known functions of FSH, revealing its involvement in broader physiological mechanisms beyond its classical reproductive role [4].

Managing PCOS effectively requires addressing the intricate relationship between metabolic dysfunction and hormonal imbalance. Available pharmacological interventions include metformin, which enhances insulin responsiveness and contributes to glycemic control; cabergoline, used to lower elevated prolactin levels; and inositol derivatives, which support ovarian function and help mitigate insulin resistance. Combined oral contraceptives (COCs) are frequently prescribed to regulate menstrual cycles and reduce androgen-related symptoms such as hirsutism and acne. For patients experiencing infertility, aromatase inhibitors are commonly employed to induce ovulation [5].

Among these therapeutic agents, metformin remains the only approved biguanide and continues to serve as a primary treatment option for PCOS, particularly in individuals with obesity and insulin resistance. Its clinical advantages include improved glucose metabolism, restoration of ovulatory function, and normalization of menstrual patterns [6]. Unlike other antidiabetic drugs, metformin is associated with a low risk of hypoglycemia, which supports its off-label application in PCOS management [7].Its mechanisms include improving insulin sensitivity, promoting weight loss, and reducing androgen levels, thereby alleviating hirsutism and menstrual irregularities [7] [8] [9]

A hallmark of polycystic ovary syndrome (PCOS) is the presence of insulin resistance, which often leads to elevated levels of circulating insulin. This persistent hyperinsulinemia stimulates androgen production within the ovarian theca cells and simultaneously suppresses hepatic synthesis of sex hormone-binding globulin (SHBG). As a result, the concentration of free, biologically active androgens increases, contributing directly to the characteristic clinical features observed in PCOS.

Metformin mitigates these metabolic disruptions by suppressing hepatic gluconeogenesis and promoting glucose uptake in peripheral tissues, ultimately leading to reduced insulin concentrations and improved endocrine balance, thereby lowering insulin levels, suppressing ovarian androgen secretion, and increasing SHBG concentrations [10].

Additionally, PCOS is characterized by dysregulated luteinizing hormone (LH) secretion, particularly increased pulse amplitude. Metformin has been shown to normalize LH pulsatility, Restoring reproductive rhythm and ovulation through adjustment of the central-peripheral hormonal axis [11]. Its role in ovulation

induction is well established, with monotherapy achieving ovulation rates of approximately 40%. When combined with clomiphene citrate, ovulation rates may reach 67%, with pregnancy occurring in nearly 69% of those who ovulate, highlighting the synergistic potential of combination therapy in enhancing fertility outcomes [12].

Although estrogen is primarily an ovarian hormone, it was measured in this study to capture its feedback regulation on pituitary gonadotropins (FSH and LH). This approach provides a more comprehensive view of the hypothalamic–pituitary–ovarian axis in PCOS and highlights the novelty of our design by simultaneously assessing pituitary and ovarian hormones under incremental metformin dosing.

Materials and Methods

• **Study Design and Setting** This forward-looking clinical investigation was carried out at Al-Zahra General Hospital in Al-Musayyib, Babylon, Iraq, spanning a six-month interval from February 1 to July 1, 2024. The primary objective was to assess how different doses of metformin influence pituitary hormone activity in women clinically diagnosed with polycystic ovary syndrome (PCOS).

• **Participants** The study cohort included 90 female patients aged 16 to 45 years, all of whom fulfilled the diagnostic criteria for PCOS as outlined by the Rotterdam consensus. This framework mandates the presence of at least two of the following features: oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and polycystic ovarian morphology confirmed via ultrasonography [13].

Participants were randomly allocated into three treatment arms:

- **Group 1:** 30 individuals received 500 mg/day of metformin
- **Group 2:** 30 individuals received 800 mg/day
- **Group 3:** 30 individuals received 1000 mg/day

Each dosage was administered in two divided doses daily over a three-month period. Additionally, a control group of healthy women of reproductive age, exhibiting regular menstrual cycles and no clinical or biochemical indicators of PCOS, was included for comparative analysis.

Hormonal Assessment Upon completion of the treatment phase, venous blood samples were obtained from all subjects to determine serum concentrations of the following hormones:

- Follicle-stimulating hormone (FSH)
- Luteinizing hormone (LH)
- Prolactin (PRL)
- Estrogen

Hormonal measurements were conducted using the enzyme-linked immunosorbent assay (ELISA) technique, adhering to standardized laboratory protocols [13].

Ethical Approval The research protocol received formal approval from the Research Ethics Committee of the College of Science, Karbala University. The study was conducted in accordance with institutional guidelines and the principles of the Declaration of Helsinki. Approval Number: 0012 CSE IN 12/5/2025.

Statistical Analysis: Quantitative variables were presented as mean ± standard deviation (SD). Intergroup comparisons were performed using the Student's t-test for continuous data. A p-value below 0.05 was considered indicative of statistical significance [14]. For future investigations involving multiple treatment arms, the use of ANOVA with post hoc testing is recommended to enhance analytical precision.

Results

Participant Distribution

Among the 90 enrolled women with PCOS, the age distribution revealed that the majority (33%) were within the 34–39

year age range, while the lowest representation (7%) was observed in the 40–45 year group. This demographic concentration aligns with the peak reproductive years commonly affected by PCOS.

Hormonal Profiles Post-Treatment

Following three months of metformin therapy, endocrine assessments were conducted using ELISA to quantify serum levels of FSH, LH, PRL, and estrogen. The results demonstrated a dose-dependent hormonal response, particularly in **Group 3** (1000 mg/day), as detailed below:

Follicle-Stimulating Hormone (FSH)

- **Pre-treatment**: 40.56 ± 7.45 µg/ml
- **Post-treatment**: 8.54 ± 1.65 µg/ml
- **Observation**: A marked reduction in FSH levels was observed in Group 3, indicating significant suppression of gonadotropic activity.

Luteinizing Hormone (LH)

- **Pre-treatment**: 30.53 ± 8.34 µg/ml
- **Post-treatment**: 11.53 ± 11.73 µg/ml
- **Observation**: LH levels declined substantially, suggesting improved regulation of the hypothalamic-pituitary-ovarian axis.

Estrogen

- **Pre-treatment**: 19.34 ± 4.67 µg/ml
- **Post-treatment**: 22.87 ± 38 µg/ml
- **Observation**: Estrogen levels showed a variable increase post-treatment, possibly reflecting restored follicular activity.

Prolactin (PRL)

- **Pre-treatment**: 4.72 ± 6.34 µg/ml
- **Post-treatment**: In Group 3, serum PRL levels increased from 4.72 ± 6.34 µg/ml to 8.64 ± 3.56 µg/ml, suggesting a stimulatory effect of metformin on prolactin secretion

• Summary of Hormonal Shifts

The data suggest that higher doses of metformin (1000 mg/day) are associated with more pronounced modulation of pituitary hormones. The reductions in FSH and LH, coupled with elevated PRL and estrogen levels, reflect a potential rebalancing of endocrine function in PCOS patients.

Table 1: Age Distribution of PCOS Patients

Age Group (Years)	**Number of Patients**	**Percentage (%)**
20–25	18	20%
26–33	24	27%
34–39	30	33%
40–45	6	7%
Total	**90**	**100%**

Note: The highest prevalence of PCOS was observed in the 34–39 age group.

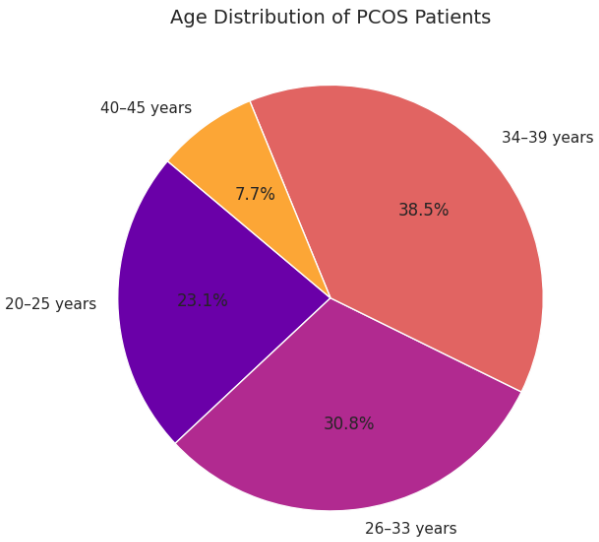

Figure 1: Age Distribution Pie Chart
A circular chart showing the proportion of patients in each age group. The 34–39 age group occupies the largest segment (33%), followed by 26–33 (27%), 20–25 (20%), and 40–45 (7%).

Table 2: Comparative Distribution of Body Mass Index (BMI) Categories Between PCOS Patients and Control Subjects

Body mass Kg/m2	Control	Patients
16-21	9 %	_
22-27	13%	10%
28-33	18%	20%
34-39	20%	25%
40-45	30%	35%

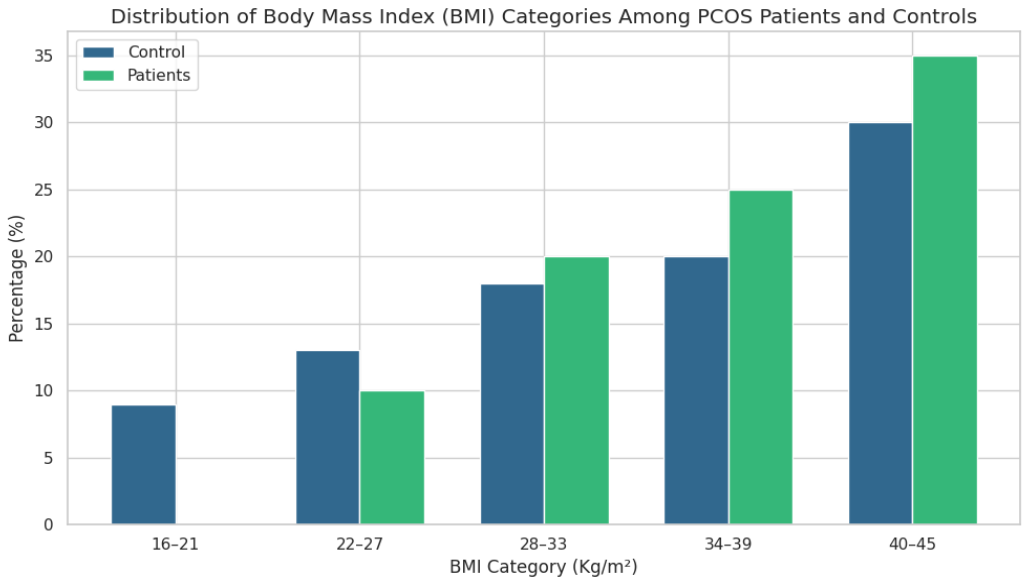

Figure 2: Grouped bar chart illustrating the percentage distribution of BMI categories among PCOS patients and control subjects. Higher BMI categories were more prevalent in the patient group.

Table 3: Dose-Responsive Hormonal Changes in PCOS Patients Treated with Metformin			
Groups	**Hormons**	**Doses Before**	**After 3 months**
Group (1) women with PCOS who received a daily dose of 500mg	FSH	40.56±7.45	11.87±4.76
	LH	30.53±8.34	15.54±3.76
	PRL	4.72±6.34	6.23±7.43
	Estrogen	10.84±4.73	19.34±4.67
Group (2) women with PCOS who received the 800mg metformin dosage months.	FSH	40.56±7.45	10.73±2.65
	LH	30.53±8.34	13.62±2.73
	PRL	4.72±6.34	7.45±4.74
	Estrogen	10.84±4.73	20.29±3.85
Group (3) women with PCOS who received the 1000mg metformin dosage	FSH	40.56±7.45	8.54±1.65
	LH	30.53±8.34	11.53±11.73
	PRL	4.72±6.34	8.64±3.56
	Estrogen	10.84±4.73	22.87±38
P - value		2.85	3.76

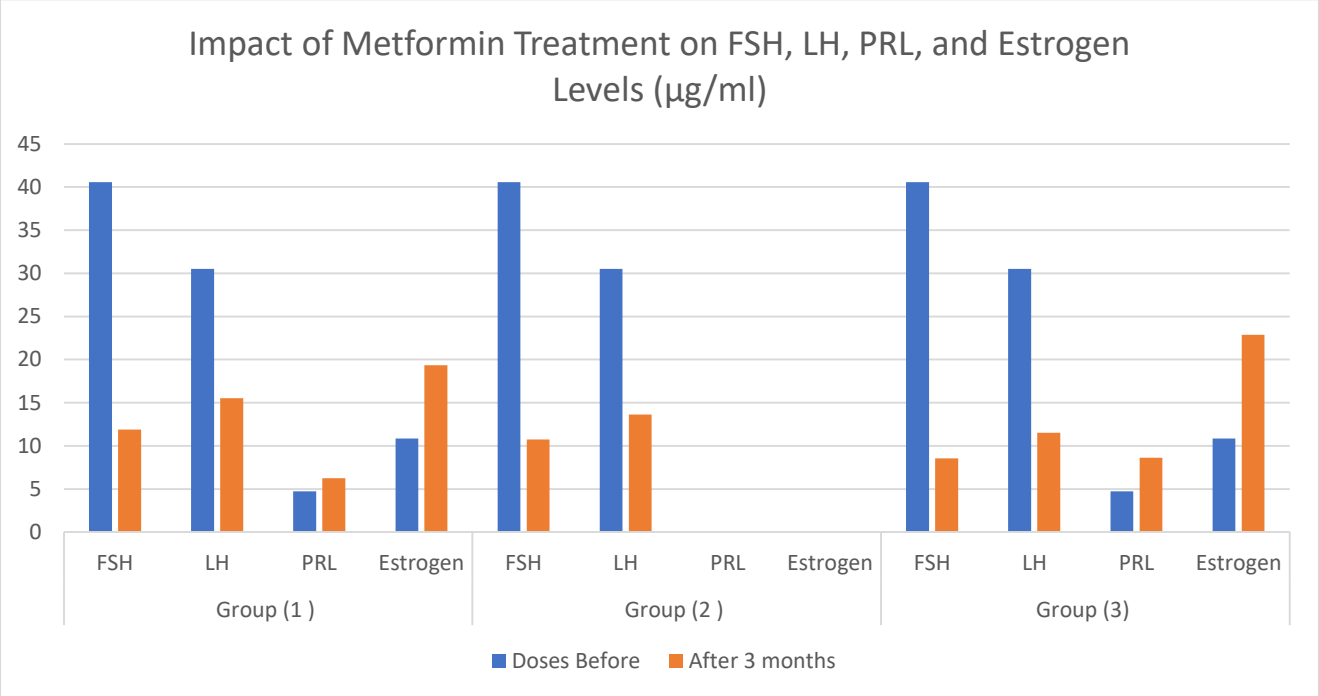

Figure 3: Effect of Metformin on Key Reproductive Hormones Over the Treatment Period

Discussion

The novelty of this study lies in its dose-comparative design, which highlights distinct endocrine responses across incremental metformin regimens. By including estrogen alongside pituitary hormones, we were able to evaluate the feedback loop between ovarian and pituitary function. This extends beyond the well-established metabolic effects of metformin, offering new perspectives on its role in central endocrine regulation.

Metformin has consistently demonstrated efficacy in alleviating hallmark symptoms of PCOS, including hirsutism, irregular menstrual cycles, and anovulation. Simultaneously, it enhances insulin sensitivity and promotes weight loss—two factors that collectively support metabolic stabilization and reproductive improvement in affected women [15].

Beyond its metabolic benefits, metformin exerts significant influence on vascular health and hormonal regulation. Notably, it reduces circulating levels of plasminogen activator inhibitor-1, a biomarker linked to endothelial dysfunction and thrombotic risk, thereby potentially improving vascular integrity [16]. These effects align with previous findings suggesting that prolonged metformin use during pregnancy in PCOS patients may lower the incidence of gestational diabetes.

Although oral contraceptives remain a conventional treatment for functional ovarian cysts due to their ability to suppress follicular development [17] [18], metformin presents a non-hormonal alternative that directly addresses the metabolic and endocrine imbalances underlying PCOS.

The present investigation supports these therapeutic perspectives by revealing a dose-dependent hormonal response to metformin. Administration of metformin at a dosage of 1000 mg/day was associated with the most significant hormonal changes, including marked reductions in serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), accompanied by elevated concentrations of estrogen and prolactin. The observed hormonal changes indicate that administering higher doses of metformin may exert a more substantial regulatory effect on the hypothalamic-pituitary-ovarian axis, thereby promoting hormonal balance and enhancing reproductive outcomes. [19]

In terms of demographic distribution, the highest prevalence of PCOS within the study cohort was noted among women aged 34 to 39 years, which corresponds with trends reported in earlier epidemiological studies [20]. Minor deviations in age-related patterns across different investigations may stem from differences in sample composition, recruitment protocols, or genetic and environmental influences [21].

Taken together, these findings affirm the clinical relevance of metformin as a dose-sensitive agent in the hormonal management of PCOS. They further underscore the importance of individualized therapeutic approaches that consider each patient's unique metabolic and reproductive characteristics.

Conclusion

By demonstrating dose-dependent modulation of pituitary hormones (FSH, LH, PRL) and ovarian estrogen, this study contributes novel evidence to the literature. It suggests that metformin’s therapeutic potential in PCOS extends to central endocrine regulation through the hypothalamic–pituitary–ovarian axis, not merely peripheral metabolic pathways.

The current investigation demonstrates a clear relationship between metformin dosage and hormonal responsiveness in women diagnosed with polycystic ovary syndrome (PCOS). Among the dosing regimens studied, the 1000 mg/day protocol elicited the most substantial endocrine alterations, characterized by suppressed levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), alongside elevated concentrations of

estrogen and prolactin. These findings point toward a dose-dependent modulation of the hypothalamic-pituitary-ovarian axis, which may contribute to restoring hormonal equilibrium and improving reproductive efficiency.

Beyond its metabolic benefits, metformin appears to influence endocrine pathways, positioning it as a multifaceted therapeutic agent in PCOS management. Personalizing the dosage based on each patient's hormonal profile could enhance treatment precision and clinical outcomes. To build on these insights, future studies with broader sample sizes and longer observation periods are essential to clarify metformin's role in reproductive endocrinology and its potential impact on fertility trajectories.

References

1. Bidwell A. Chronic fructose ingestion as a major health concern: Is a sedentary lifestyle making it worse? A review. *Nutrients*. 2017;9(6):549. doi:10.3390/nu9060549
2. Swaroop A, Jaipuriar AS, Gupta SK, Bagchi M, Kumar P, Preuss HG, et al. Efficacy of a novel fenugreek seed extract (Trigonella foenum-graecum, Furocyst™) in polycystic ovary syndrome (PCOS). *Int J Med Sci*. 2015;12(10):825–31. doi:10.7150/ijms.12932
3. Bottomley C, Bourne T. Diagnosis and management of ovarian cyst accidents. *Best Pract Res Clin Obstet Gynaecol*. 2009;23(5):711–24. doi:10.1016/j.bpobgyn.2009.01.005
4. Brassard M, AinMelk Y, Baillargeon JP. Basic infertility including polycystic ovary syndrome. *Med Clin North Am*. 2008;92(5):1163–92. doi:10.1016/j.mcna.2008.04.007
5. Moran LJ, Tassone EC, Boyle J, Brennan L, Harrison CL, Hirschberg AL, et al. Evidence summaries and recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome: Lifestyle management. *Obes Rev*. 2020;21(10):e13046. doi:10.1111/obr.13046
6. Maruthur NM, Tseng E, Hutfless S, Wilson LM, Suarez-Cuervo C, Berger Z, et al. Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: A systematic review and meta-analysis. *Ann Intern Med*. 2016;164(11):740–51. doi:10.7326/M15-2650
7. Triggle CR, Ding H. Metformin is not just an antihyperglycaemic drug but also has protective effects on the vascular endothelium. *Acta Physiol*. 2017;219(1):138–51. doi:10.1111/apha.12727
8. Hundal RS, Inzucchi SE. Metformin: New understandings, new uses. *Drugs*. 2003;63(18):1879–94. doi:10.2165/00003495-200363180-00003
9. Kocer D, Bayram F, Diri H. The effects of metformin on endothelial dysfunction, lipid metabolism and oxidative stress in women with polycystic ovary syndrome. *Gynecol Endocrinol*. 2014;30(5):367–71. doi:10.3109/09513590.2013.875145
10. Galindo García CG, Vega Arias MJ, Hernández Marín I, Ayala AR. [Mechanism of action of insulin sensitizer agents in the treatment of polycystic ovarian syndrome]. *Ginecol Obstet Mex*. 2007;75(3):148–54.
11. Omran MYS. Metformin and polycystic ovary syndrome. *Int J Health Sci (Qassim)*. 2007;1(1):75–80.
12. Dutta S, Shah RB, Singhal S, Dutta SB, Bansal S, Sinha S, et al. Metformin: A review of potential mechanism and therapeutic utility beyond diabetes. *Drug Des Devel Ther*. 2023;17:1907–32. doi:10.2147/DDDT.S408065

13. Sharma S, Mathur DK, Paliwal V, Bhargava P. Efficacy of metformin in the treatment of acne in women with polycystic ovarian syndrome: A newer approach to acne therapy. *J Clin Aesthet Dermatol*. 2019;12(5):34–8.
14. Attia GM, Almouteri MM, Alnakhli FT. Role of metformin in polycystic ovary syndrome (PCOS): Related infertility. *Cureus*. 2023 Aug 31 [cited 2025 Mar 25]; Available from: https://www.cureus.com/articles/167371-role-of-metformin-in-polycystic-ovary-syndrome-pcos-related-infertility
15. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *N Engl J Med*. 1998;338(26):1876–80. doi:10.1056/NEJM199806253382602
16. Zendron C, Gonçalves HF, Cavalcante FS, Pereira TR, Evangelista A, Ramos CF, et al. Increased expression of the leptin receptor in human ovaries affected by endometrioma and detection of high levels of leptin in the ovarian endometriomal fluid. *J Ovarian Res*. 2014;7(1):2. doi:10.1186/1757-2215-7-2
17. Bril F, Ezeh U, Amiri M, Hatoum S, Pace L, Chen YH, et al. Adipose tissue dysfunction in polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2023;109(1):10–24. doi:10.1210/clinem/dgad608
18. Qiao J, Feng HL. Extra- and intra-ovarian factors in polycystic ovary syndrome: Impact on oocyte maturation and embryo developmental competence. *Hum Reprod Update*. 2011;17(1):17–33. doi:10.1093/humupd/dmq034
19. Qu X, Donnelly R. Sex hormone-binding globulin (SHBG) as an early biomarker and therapeutic target in polycystic ovary syndrome. *Int J Mol Sci*. 2020;21(21):8191. doi:10.3390/ijms21218191
20. Owens LA, Kristensen SG, Lerner A, Christopoulos G, Lavery S, Hanyaloglu AC, et al. Gene expression in granulosa cells from small antral follicles from women with or without polycystic ovaries. *J Clin Endocrinol Metab*. 2019;104(12):6182–92. doi:10.1210/clinem/dgz111
21. Moran LJ, Ranasinha S, Zoungas S, McNaughton SA, Brown WJ, Teede HJ. The contribution of diet, physical activity and sedentary behaviour to body mass index in women with and without polycystic ovary syndrome. *Hum Reprod*. 2013;28(8):2276–83. doi:10.1093/humrep/det263