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Metformin-dose-dependent effect on both pituitary hormones and vitamin D levels in women with PCOS in Kerbala

Nada Abdulhussein Alkafaji*[1]

[1]Department of Food Science , College of agriculture, university of kerbala, Iraq.
* nada.a@uokerbala.edu.iq

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ABSTRACT

The relevance of research is to determine the impact of metformin dosages on vitamin D, estrogen, PRL, LH and FSH concentrations in women with PCOS in Kerbala. In this research, eighty females between ages 20 and 40 were used. Between February 2, 2025, and August 15, 2025, women came to the Indian General Hospital in Kerbala. Subjects were grouped into four different groups. G1: Group of 20 females diagnosed with Polycystic Ovaries who were given 250 mg metformin three times daily for four months. G2: Group of 20 females with PCOS who were given metformin dose of 500 mg three times daily for four months.G3: Group of 20 females diagnosed with PCOS were given 800mg metformin three times daily for four months. G4: Group of 20 females with PCOS were prescribed to take a metformin dosage of 1000 mg thrice daily for four months. Serum testing was conducted five months post-administration of the drugs using ELISA test for FSH, LH, PRL, Estrogen, and vitamin D levels. show that metformin at G4 with a dose of 1000 mg three times daily for 4 months has a significant effect on vitamin D ,estrogen, PRL, LH and FSH concentrations.

Keywords: Polycystic Ovary Syndrome , Metformin, Vitamin D, Pituitary hormones.

1.Introduction

Polycystic Ovary Syndrome (PCOS) stands as one of the most prevalent endocrine and metabolic disorders affecting women of reproductive age globally [1]. It is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. PCOS pathophysiology is closely associated with insulin resistance and hyperinsulinemia [2]. In the context of this case study, Metformin, a biguanide insulin sensitizer, has been identified as the main off-label drug treatment modality in an effort to ensure that patients achieve metabolic health and ovulatory functions [3]. However, the role played by Metformin within the body goes beyond that [4]. Metformin is thought to influence the HPO axis depending on its dose [5].

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Specifically, the impact of the drug on TSH and Prolactin has been investigated extensively due to the ability of Metformin to modify pituitary hormone sensitivity and secretion through AMPK activation. Information regarding the effect of various dosages of the drug on TSH and Prolactin can prove extremely useful in obtaining endocrine outcomes [6]. Importantly, emerging research suggests that the endocrine effects of metformin may be dose-dependent. higher therapeutic doses (commonly 1500–2550 mg/day) appear to produce more pronounced improvements in insulin resistance indices and reproductive hormonal profiles compared with lower doses, although interindividual variability remains considerable. this raises critical questions regarding the optimal dosing strategy required to achieve meaningful modulation of pituitary hormones particularly LH and FSH among women at risk for or diagnosed with PCOS[7]. Concurrently, Vitamin D deficiency is highly prevalent among women with PCOS and has been implicated in the exacerbation of insulin resistance, menstrual irregularity, and hyperandrogenism [8]. Vitamin D receptors are expressed in ovarian and pituitary tissues, suggesting a regulatory role in reproductive endocrinology. Several systematic reviews have indicated that vitamin D supplementation may improve menstrual regularity, androgen levels, and metabolic parameters in women with PCOS. furthermore, combined therapy with metformin and vitamin D has demonstrated additive or synergistic effects on metabolic and hormonal outcomes compared with metformin alone [9,10]. The interplay between metformin dosage, pituitary hormone regulation, and vitamin D status thus represents a complex but clinically significant axis in PCOS management. Vitamin D deficiency may potentially attenuate therapeutic responsiveness to metformin, while adequate vitamin D levels could enhance endocrine and metabolic improvements [11,12], However, despite growing interest, the specific relationship between metformin dose and its direct impact on pituitary hormones particularly within the context of varying vitamin D status remains insufficiently characterized [13,14]. The importance of this study is to determine metformin-dose-dependent effect on both pituitary hormones and vit. D levels in women with PCOS in Karbala.

2. Material and method

In this study, eighty women between the ages of twenty and forty participated. where, depending on height, their body mass index (BMI) indicates a weight of roughly 56 to 107 kg. Indian General Hospital in Kerbala provided care for women between 2/2/2025 and 8/9/2025.

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The participants were classified into four categories .

Group 1: 20 patients with PCOS on 250 mg metformin thrice daily for four months .Group 2: 20 patients with PCOS on 500 mg metformin thrice daily for four months .Group 3: 20 patients with PCOS on 800 mg metformin thrice daily for four months. Group 4: 20 patients with PCOS on 1000 mg metformin thrice daily for four months [15]. PCOS diagnosis is done based on Rotterdam criteria, and this occurs if any two out of the following three criteria are present: oligo-/anovulation, clinical/biochemical hyperandrogenism, and polycystic ovaries on ultrasonography[16]. The control group was made up of healthy women within the reproductive age range, who had regular menstrual cycles and exhibited no other PCOS symptoms. They were visiting the clinic for a general check-up [16]. Four months into the treatment process, the blood serum was tested again using ELIZA to check for hormones (FSH, LH, PRL, estrogen, and vitamin D) [17].

Statistical Analysis

They are presented as Mean ± Standard Deviation (SD) and P-value less than 0.05 for continuous variables and using the one-way a nova program [18].

4. Results

Indicate results at table 1 and figures 1,2 at G1, G2, G3, G4 to find significant increase in FSH hormone after 4 months was (12.74 , 11.24, 10.74 and 9.45 µg/mL), compared treatments before was (40.65, 39.83, 38.64 and 36.45 µg/mL), while LH hormone at figure 3 after 4 months of treatments was (17.65,16.35,15.65 and 14.36 µg/mL), compared treatments before was (31.74, 30.74, 29.76 and 27.34µg/mL), PRL hormone at figure 4 after 4 months of treatments was (5.64, 6.63, 7.87 and 8.87µg/mL) compared treatments before of treatments was (3.74, 3.54, 3.42 and 13.28 µg/mL), estrogen hormone at figure 5 after 4 months of treatments was (19.76, 20.34, 22.7, 23.74 µg/mL) compared treatments before of treatments was (10.65 , 9.35 , 9.22 and 9.37 µg/mL) vitamin D at figure 6 after 4 months of treatments was (20.45 , 21.74, 22.74 and 23.65µg/mL). Compared treatments before of treatments (10.45, 11.34, 11.65 and 12.43µg/mL).

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Table1. The impact of metformin dosages on vitamin D, estrogen, PRL, LH and FSH concentrations.

Groups	The variable	Before treatments	After 4 months of treatment
G1	FSH	**40.65**±6.64[a]	**12.74**±2.65[a]
	LH	**31.74**±4.75[a]	**17.65**±3.53[a]
	PRL	3.**74**±5.56[b]	**5.64**±4.54[a]
	Estrogen	**10.65**±4.34[b]	**19.76**±3.45[a]
	D V.	**10.45**±3.34[c]	**20.45**±4.34[d]
Group 2	FSH	3**9.83**±2.54[d]	1**1.24**±5.34[c]
	LH	**30.74**±3.64[a]	**16.35**±4.46[b]
	PRL	3.**54**±3.65[a]	**6.63**±3.54[b]
	Estrogen	**9.35**±3.34[b]	**20.34**±3.65[b]
	D V.	1**1.34**±2.64[b]	2**1.74**±4.65[a]
Group 3	FSH	**38.64**±2.54[c]	**10.74**±5.65[a]
	LH	**29.76**±3.54[c]	**15.65**±4.65[a]
	PRL	**3.42**±4.35[a]	**7.87**±3.56[a]
	Estrogen	**9.22**±2.54[a]	**22.74**±4.65[c]
	D V.	**11.65**±3.65[a]	**22.74**±3.75[c]
Group 4	FSH	**36.45**±4.74[b]	**9.45**±4.64[b]
	LH	**27.34**±5.34[b]	**14.36**±3.65[b]
	PRL	**3.28**±3.76[c]	**8.87**±2.56[a]
	Estrogen	**9.37**±4.54[c]	**2374.**±4.34[a]
	D V.	12.43±3.65[a]	**2474.**±3.65[a]
P value		1.65	3.45

Means with different letters in the same column are significantly different ($P < 0.05$) based on LSD test.

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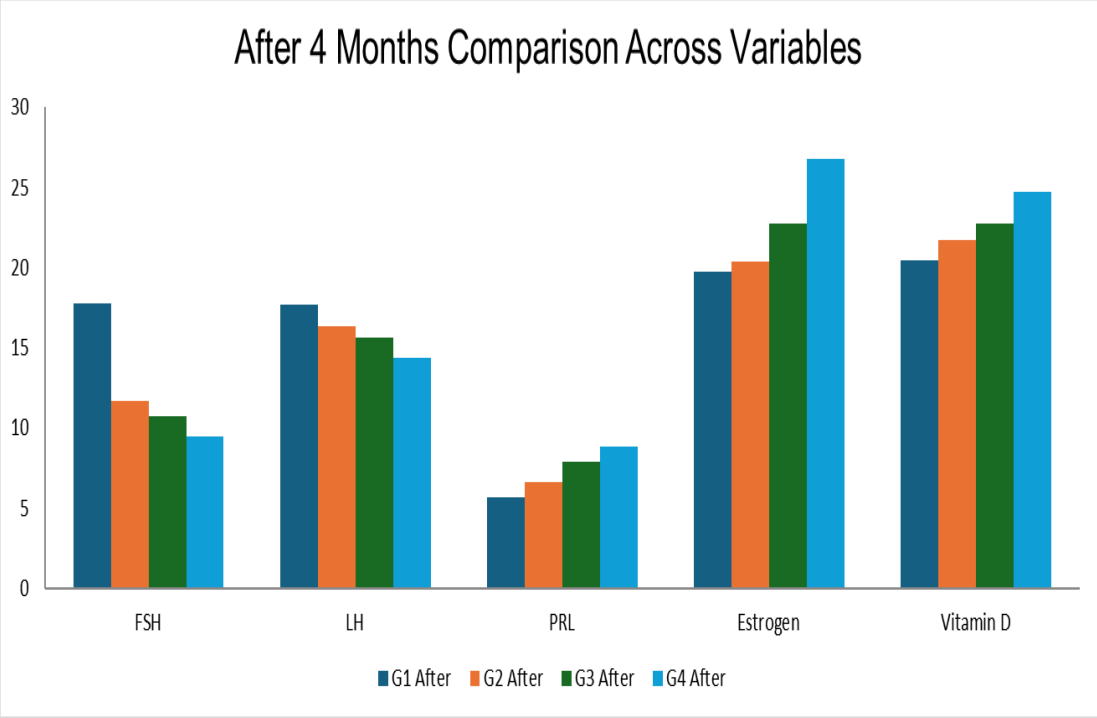

Figure 1. Metformin-dose-dependent effect on both pituitary hormones and vit. D levels

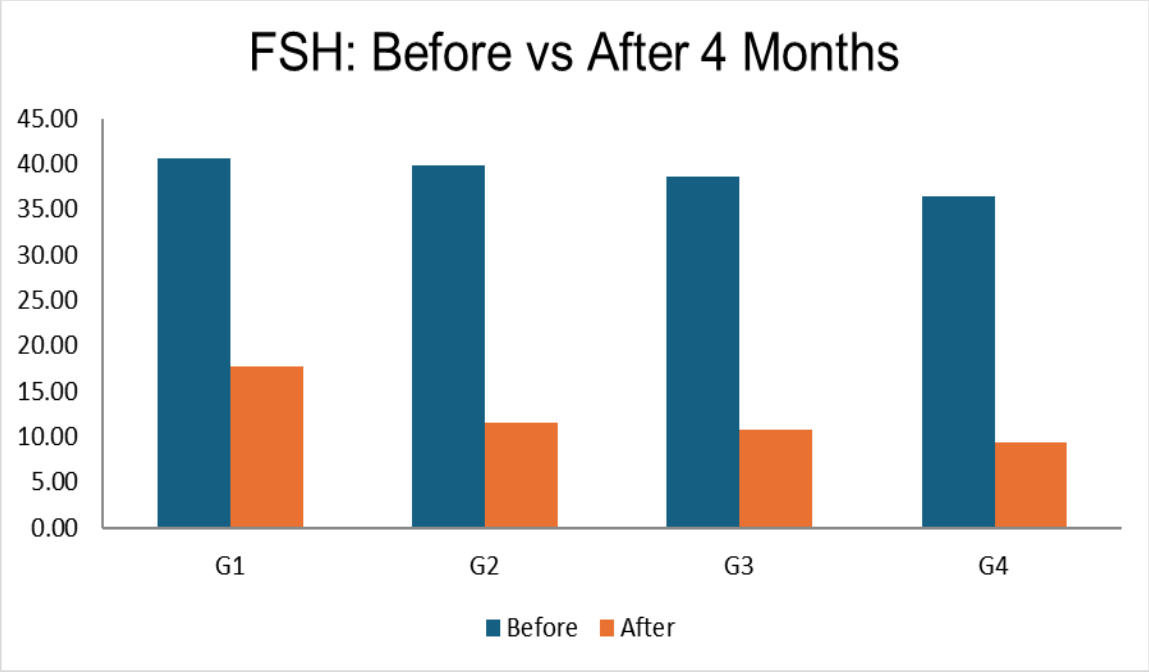

Figure 2. Metformin-dose-dependent effect on the FSH levels .

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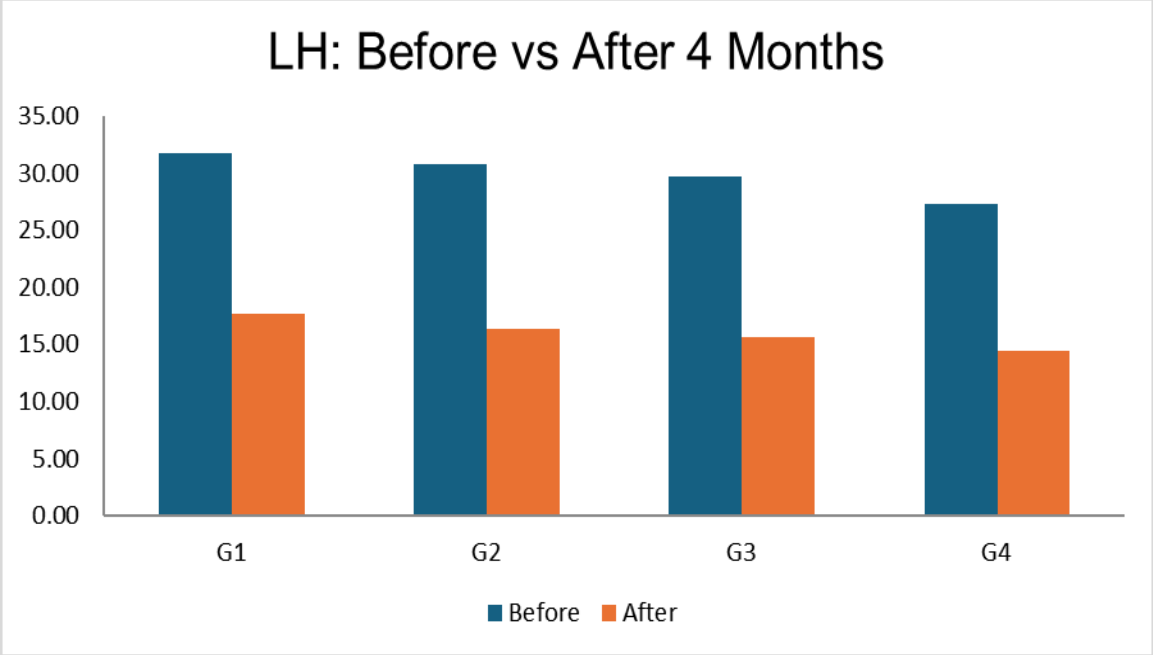

Figure 3. Metformin-dose-dependent effect on the LH levels .

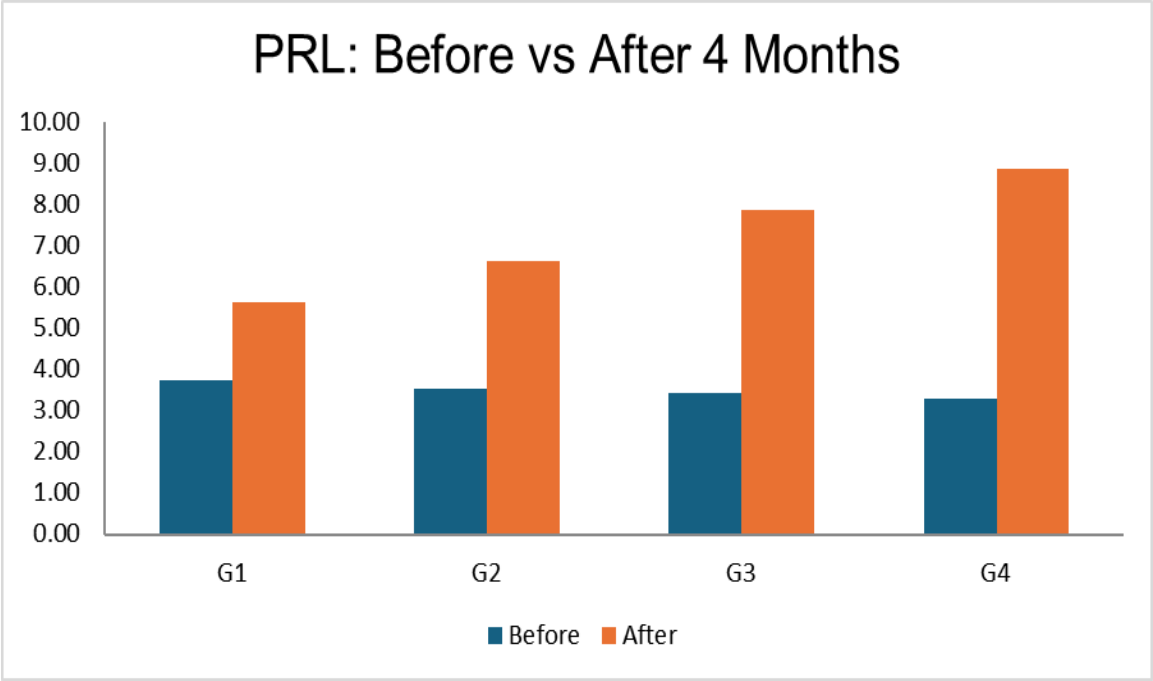

Figure 4. Metformin-dose-dependent effect on the PRLlevels

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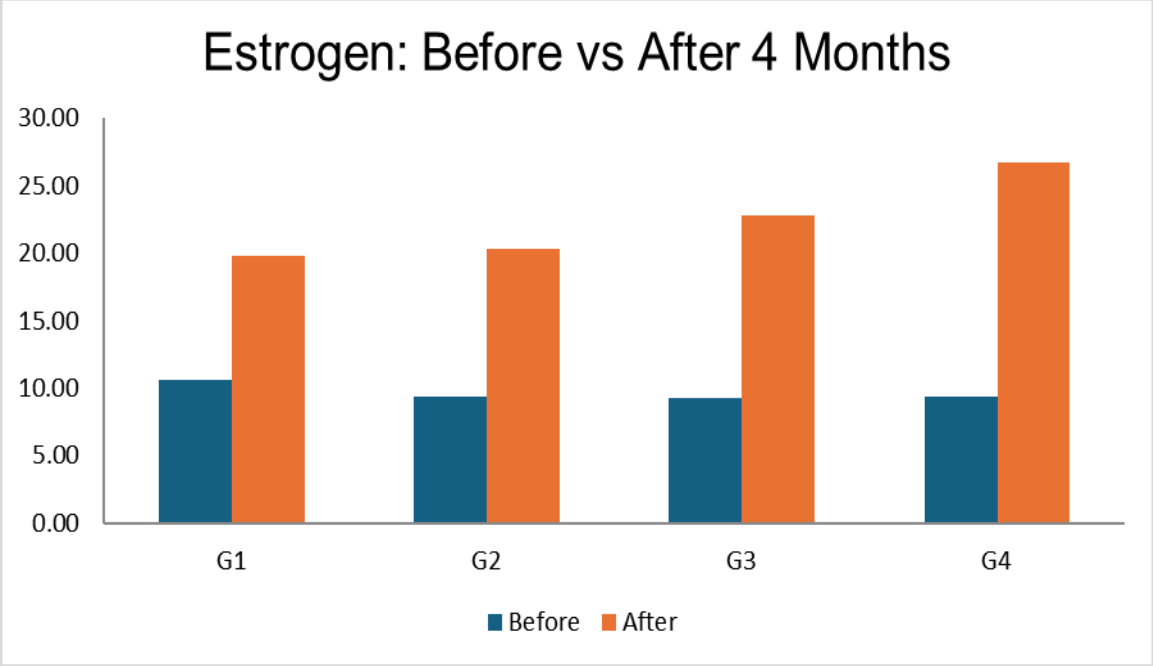

Figure 5. Metformin-dose-dependent effect on the estrogen levels

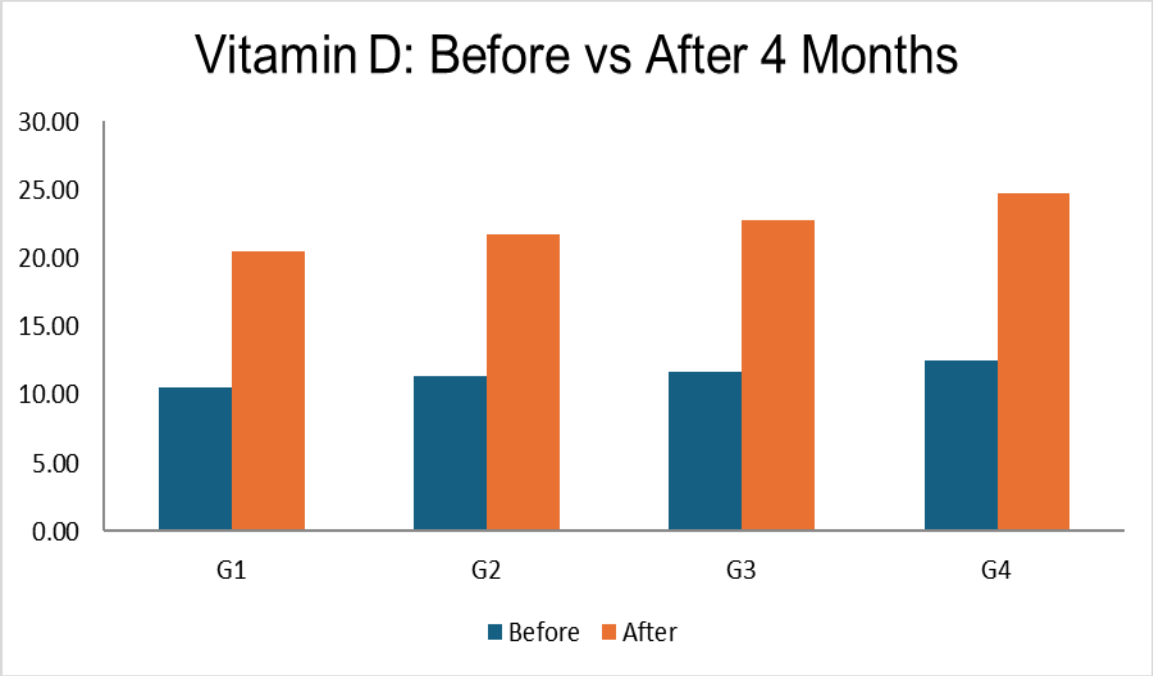

Figure 6. Metformin-dose-dependent effect on the Vitamin D.

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4. Discussion

The present findings support the concept that Metformin exerts dose-dependent modulator effects on pituitary hormonal dynamics in women with Poly cystic Ovary Syndrome (PCOS)[19] given that exaggerated LH pulsation and an elevated LH/FSH ratio are characteristic neuroendocrine features of PCOS, the observed normalization following metformin therapy reinforces the hypothesis that insulin resistance plays a central role in hypothalami–pituitary regulations[20]. Mechanistically, metformin insulin-sensitizing action likely reduces hyper insulin ovarian androgen production, this study partly or fully in agreement with previous findings indicating that higher therapeutic doses (≥1500 mg/day) are associated with more pronounced improvements in reproductive endocrine parameters compared with lower doses. This suggests that sub-therapeutic dosing may fail to adequately modulate the metabolic–endocrine interface central to PCOS pathophysiology[21]. An equally important finding relates to the interaction between metformin therapy and Vitamin D status. Vitamin D deficiency is highly prevalent among women with PCOS and has been linked to worsened insulin resistance, hyper androgenism, and menstrual irregularities. This observation supports emerging evidence that vitamin D may function as a modulator factor in endocrine responsiveness[22]. The biological plausibility of this interaction is supported by the presence of vitamin D receptors (VDR) in ovarian and pituitary tissues, suggesting a regulatory role in steroidogenesis and gonadotropin secretion. Vitamin D has also been implicated in improving insulin receptor expression and pancreatic β-cell function, which may synergistic enhance metformin insulin-sensitizing effects. therefore, inadequate vitamin D levels could attenuate the full therapeutic potential of metformin on both metabolic and pituitary outcomes[23]. From a clinical perspective, these findings highlight the importance of individualized therapeutic strategies in PCOS management. optimizing metformin dosage while simultaneously assessing and correcting vitamin D deficiency may enhance endocrine outcomes, particularly in women exhibiting pronounced neuroendocrine imbalance. this integrated approach aligns with the contemporary view of PCOS as a multi system disorder requiring combined metabolic and endocrine interventions rather than isolated symptomatic treatment[24, 25].

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5.Conclusion

This study concluded that a metformin dose of 1000 mg for four months has a significant effect on pituitary hormones and vitamin D compared to other doses.

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