Serum kisspeptin levels in women with polycystic ovary syndrome: A systematic review and meta-analysis

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ABSTRACT

Introduction: Kisspeptin is a key regulator of the hypothalamic–pituitary–gonadal axis and has been implicated in the pathophysiology of polycystic ovary syndrome (PCOS). However, reported associations between kisspeptin levels and PCOS have been inconsistent.

Materials and Methods: A systematic search of PubMed, Scopus, and Web of Science was performed from inception to August 2025 for studies comparing serum kisspeptin concentrations between PCOS patients and controls. Data extraction was conducted independently by two reviewers. A random-effects meta-analysis was used to calculate pooled standardized mean differences (SMD) with 95% confidence intervals (CI). Heterogeneity was assessed using the Q statistic and I² index. Meta-regression was performed to examine BMI as a predictor of kisspeptin levels.

Results: Twenty studies involving 670 participants were included. Pooled analysis demonstrated significantly higher serum kisspeptin levels in PCOS patients compared with controls (SMD = 0.511; 95% CI: 0.376–0.646; $p < 0.001$; $I^2 = 0\%$). Meta-regression revealed that BMI significantly moderated the association, with overweight/obese PCOS patients showing the greatest elevation in kisspeptin concentrations ($\beta = 0.756$; 95% CI: 0.483–1.029; $p < 0.001$).

Conclusion: Serum kisspeptin levels are elevated in women with PCOS, particularly among those with overweight/obese BMI, suggesting a possible interaction between metabolic status and reproductive neuroendocrine regulation. These findings support the potential of kisspeptin as a biomarker for PCOS and highlight the need for further research into its mechanistic role and clinical applicability.

KEYWORDS:
Body mass index, kisspeptin, polycystic ovary syndrome

INTRODUCTION

Polycyclic ovary syndrome (PCOS) is a frequent endocrine disorder that happens in women at the age of reproductive life which is estimated to reach 6-20 percent around the world based on the diagnostic standards that flow on the Rotterdam, NIH, and AE-PCOS criteria.[1] The disease has a wide variable clinical characteristic with a central feature of chronic anovulation, hyperandrogenism and the ovarian character of massive cysts seen on ultrasound imaging.[1-2] Metabolic imbalances, such as insulin resistance, being overweight/obese, dyslipidemia, and increased chances of developing type 2 diabetes mellitus are also associated with PCOS.[1,3] Despite its high rate of prevalence and multifactorial phenotype, its pathophysiological mechanisms are not fully described, which reduces the ability not only to make an adequate diagnosis but also to implement effective treatment options accordingly.

The neuropeptide, kisspeptin, encoded by KISS1 has gained more and more acceptance as a central modulator of the hypothalamicpituitarygonadal (HPG) axis through its activating effect on gonadotropin-releasing hormone (GnRH) release.[4] When kisspeptin binds to its receptor, GPR54 (also called KISS1R), expression is facilitated on GnRH neurons, which in turn stimulates the release of luteinizing hormone(LH) and follicle-stimulating hormone (FSH).[4-5] This signaling cascade is necessary to not only the induction of puberty, but required to sustain reproductive capacity as well. As a result, impairment of kisspeptin-GPR54 signaling is the basis of a range of reproductive pathologies, such as hypogonadotropic hypogonadism, precocious puberty, and infertility.[4-5] Considering the primary position of GnRH in the process of ovarian functioning, deviations either in the levels or the activity of kisspeptin will account for the hormonal and ovulatory disturbances that dominate this complicated clinical picture of PCOS.

Several studies have investigated serum kisspeptin levels in women with PCOS, aiming to elucidate its potential role in the disorder's pathogenesis.[6-7] However, the results have been inconsistent: some studies report elevated kisspeptin concentrations in PCOS patients, possibly reflecting increased GnRH pulse frequency and LH hypersecretion, while others find no significant differences or even reduced levels, suggesting altered feedback mechanisms. These discrepancies may stem from differences in study populations, diagnostic criteria, assay methodologies, and confounding factors such as body mass index (BMI), insulin resistance, and androgen levels. Such heterogeneity highlights the need for a

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systematic synthesis of the evidence to better understand the relationship between kisspeptin and PCOS.[6,8]

A comprehensive meta-analysis can quantitatively assess the existing data, address variability among studies, and provide more precise estimates of the association between kisspeptin levels and PCOS. By pooling data from multiple studies, this approach may clarify whether kisspeptin is consistently altered in PCOS and explore potential modifiers of this relationship, such as BMI, assay technique, or regional differences. Understanding this relationship is not only relevant to elucidating PCOS pathophysiology but may also inform the development of novel diagnostic biomarkers and therapeutic targets. This systematic review and meta-analysis therefore aims to evaluate and synthesize current evidence on serum kisspeptin levels in women with PCOS compared to healthy controls.

MATERIALS AND METHODS

This study followed the PRISMA 2020 guidelines for conducting and reporting systematic reviews and meta-analyses. The review protocol was developed a priori and registered in PROSPERO to ensure transparency and reduce potential for bias.

Studies were considered eligible if they:

1. Included reproductive-age women with diagnosed PCOS (Rotterdam, NIH, or AES criteria) and a healthy control group;
2. Reported serum or plasma kisspeptin levels;
3. Employed observational study designs (case-control or cross-sectional);
4. Reported data sufficient to compute effect sizes (means with SD or equivalent).

Excluded were: animal or in vitro studies, reviews, conference abstracts without full texts, and studies lacking necessary quantitative data.

We systematically searched PubMed, Scopus, Web of Science, and Cochrane Library from inception to 2025. Search terms included variations of (“kisspeptin” OR “metastin”) AND (“PCOS” OR “polycystic ovary syndrome”). Citation lists of relevant articles and reference lists were manually screened for additional studies.[9]

Titles and abstracts were screened independently by two reviewers. Full texts of potential studies were assessed for eligibility. Discrepancies were resolved by consensus or a third reviewer. The study selection process is summarized using a PRISMA flow diagram.

Reviewer independently extracted data into a standardized form, including: author, publication year, country, sample sizes, age, BMI, diagnostic criteria, kisspeptin measurement method (e.g., ELISA), and mean ± SD levels. Any discrepancies were discussed and resolved.

Study quality was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies. Criteria included selection of participants, comparability of groups, and ascertainment of exposure/outcome.[10]

We calculated pooled standardized mean differences (SMDs) with 95% confidence intervals using a random-effects model. Heterogeneity was evaluated using the I^2 statistic. Pre-specified subgroup analyses were conducted based on BMI category, diagnostic criteria used, and assay method. Sensitivity analyses and assessment of publication bias (funnel plot, Egger’s test) were also performed.[11-12]

RESULTS

A total of 1,591 records were identified from databases (n = 1,506) and trial registers (n = 85). Additional records were obtained from websites (n = 12), organizations (n = 5), and citation searching (n = 2). After removing duplicates, 740 records were screened by title and abstract, with 451 reports sought for retrieval. Of these, 257 reports were assessed for eligibility, resulting in the inclusion of 16 new studies (2 reports). Combined with the 17 studies (5 reports) from the previous version of the review, the final analysis included 18 studies (21 reports). Figure 1 shows the PRISMA flow diagram for study selection.

The heterogeneity test ($Q_e(20) = 36.76$, $p = 0.013$) indicates statistically significant variability in effect sizes across the included studies, suggesting that the observed differences are unlikely to be due to sampling error alone. This finding implies the presence of potential moderators or study-level characteristics influencing the effect size. The pooled effect size was statistically significant ($t(20) = 5.27$, $p < 0.001$), confirming a robust overall association between the studied variables across all included datasets.

The pooled effect size was estimated at 0.586 (95% CI: 0.354 to 0.818), indicating a moderate and positive association between the variables of interest. The 95% prediction interval ranged from –0.160 to 1.331, suggesting that while most future studies are xpected to yield positive effects, there remains the possibility of obtaining negligible or even negative effects under certain conditions (Table I).

The between-study standard deviation (τ) was 0.340, and the between-study variance (τ^2) was 0.115, pointing to notable dispersion of true effect sizes. The I^2 statistic was 45.78% (95% CI: 7.00% to 74.74%), reflecting moderate heterogeneity, while the H^2 value of 1.844 suggests that the total variability is approximately 1.84 times greater than what would be expected from sampling error alone. These heterogeneity metrics reinforce the conclusion from the Q test that variability among studies warrants further exploration, potentially via meta-regression or subgroup analyses (Figure 2).

The residual heterogeneity test ($Q_e(19) = 12.32$, $p = 0.871$) was not statistically significant, indicating that the variability in effect sizes remaining after accounting for the moderator is consistent with sampling error alone. This suggests that the included moderator explains most of the between-study variance. The pooled effect was statistically significant ($t(19) = 7.92$, $p < 0.001$), reflecting a consistent and substantial association across studies. The moderation test ($F(1, 19) = 33.71$, $p < 0.001$) confirmed that the moderator variable had a statistically significant influence on the effect size estimates.

Table I: Meta-Analytic estimates of the review

	Estimate	95% CI		95% PI	
		Lower	Upper	Lower	Upper
Pooled effect	0.586	0.354	0.818	-0.16	1.331
τ	0.34	0.101	0.636		
τ^2	0.115	0.01	0.405		
I^2	45.777	6.997	74.735		
H^2	1.844	1.075	3.958		

Table II: Effect Size Meta-Regression Coefficients

	Estimate	Standard Error	95% CI		t	df	p
			Lower	Upper			
Intercept	0.187	0.086	0.007	0.366	2.18	19	0.042
BMI Category (Overweight and Obese I-II)	0.756	0.13	0.483	1.029	5.806	19	< .001

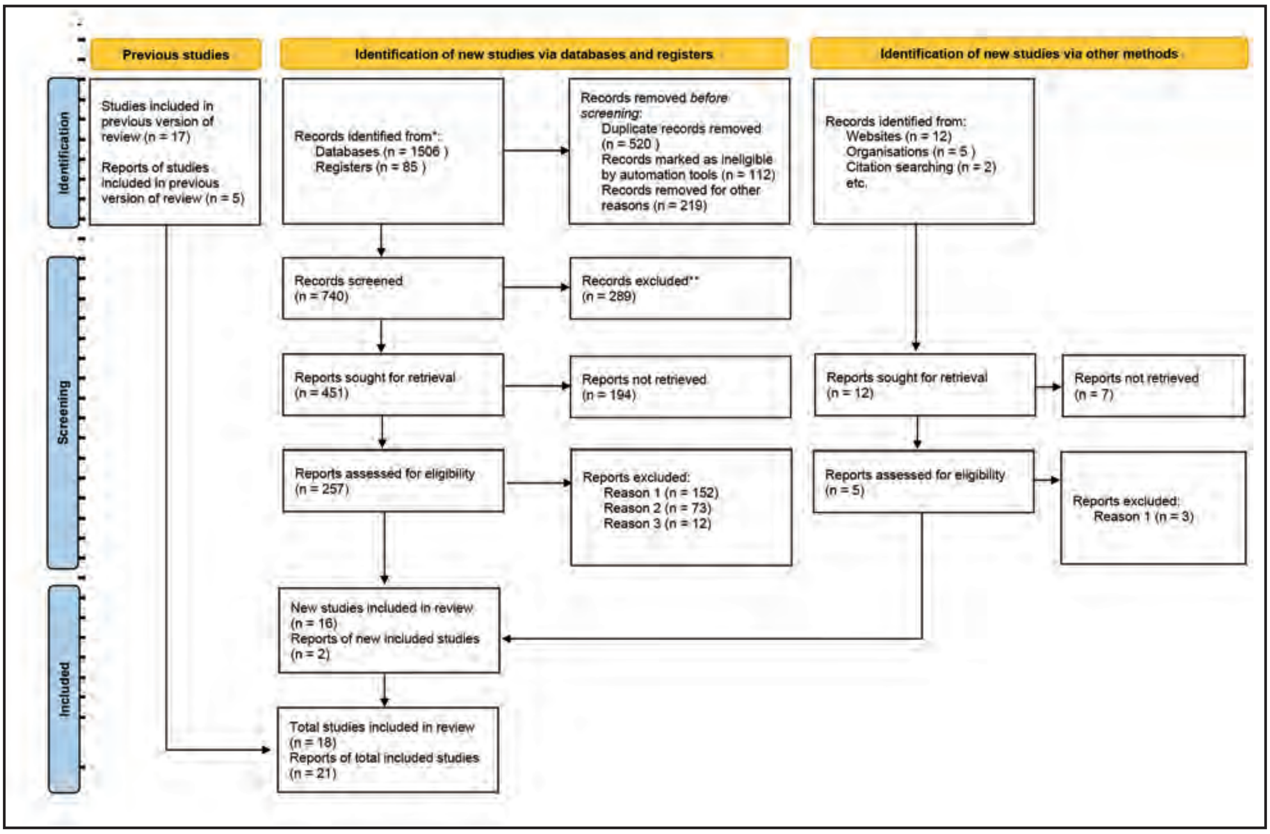

Fig. 1: PRISMA Flow Diagram

The pooled effect size was 0.511 (95% CI: 0.376 to 0.646), indicating a moderate positive association between the variables under study. The 95% prediction interval matched the confidence interval (0.376 to 0.646), implying that future studies under similar conditions are expected to yield effect sizes within this range, with minimal risk of extreme deviation.

The between-study standard deviation (τ) and variance (τ^2) were both estimated at zero, with upper confidence bounds of 0.231 and 0.053, respectively, suggesting negligible heterogeneity after accounting for the moderator. Similarly, the I^2 statistic was 0% (95% CI: 0% to 28.17%), and H^2 was 1.00 (95% CI: 1.00 to 1.39), further confirming the absence of meaningful residual variability across studies. These results indicate that the observed effects are highly consistent once the moderator is included in the model.

The omnibus test for the moderator variable “BMI Category” was statistically significant ($F(1, 19) = 33.71$, $p < 0.001$), based on the Knapp and Hartung adjustment. This indicates that BMI category explains a substantial proportion of the variance in effect sizes across studies (Table II and Figure 3).

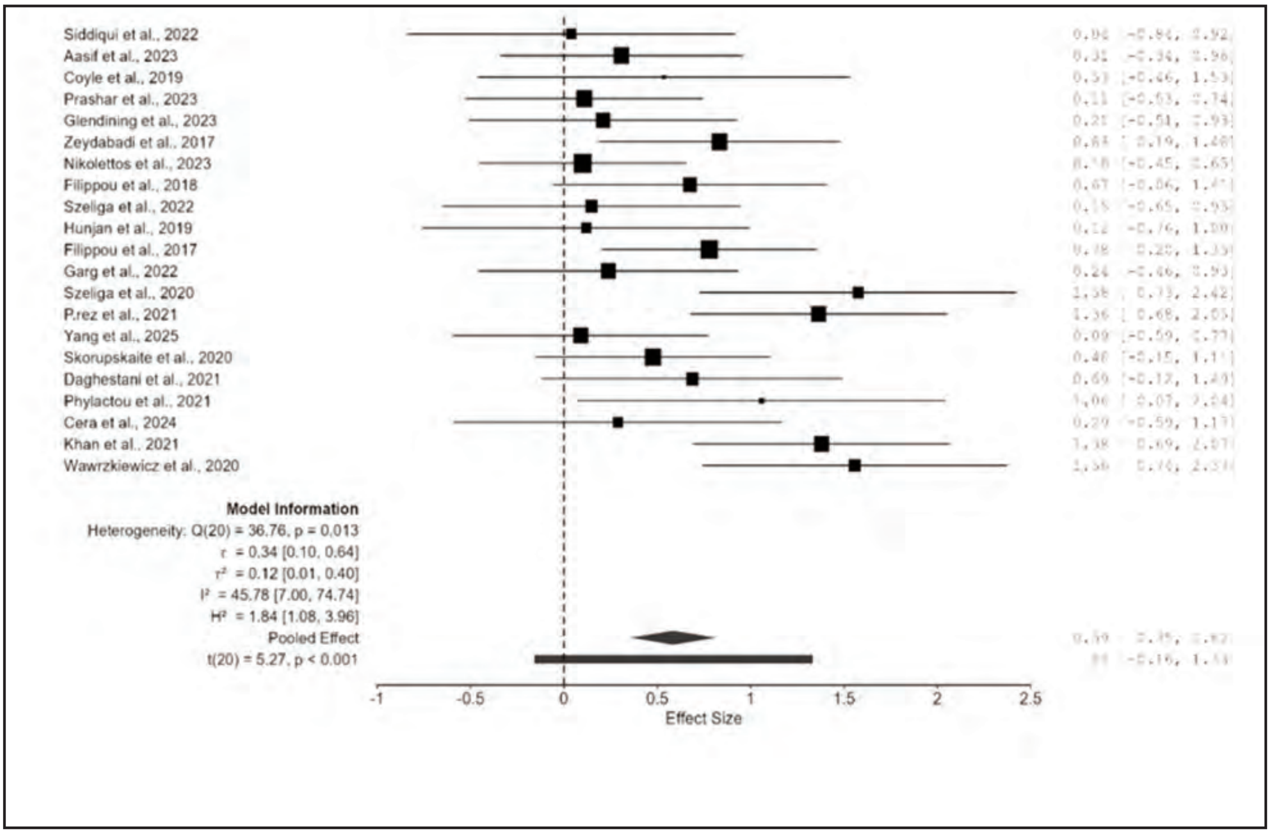

Fig. 2: Forest Plot[13-33]

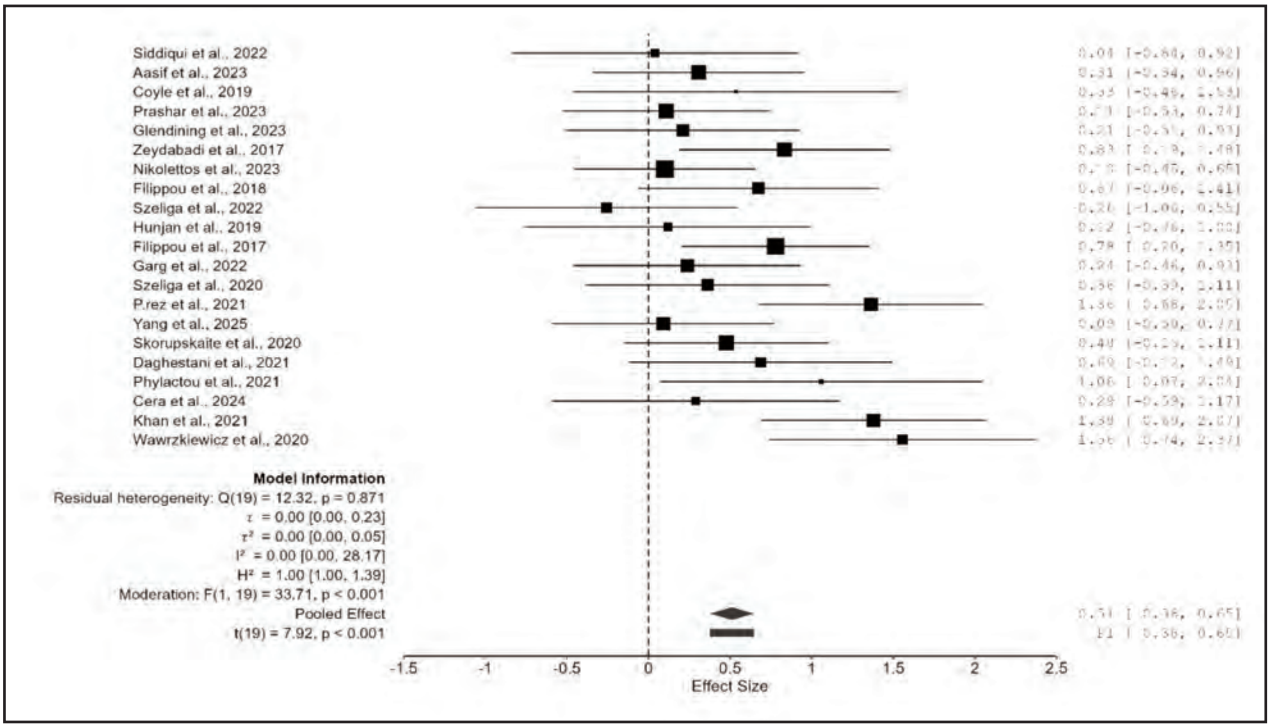

Fig. 3: Forest Plot of Regression Effect[13-33]

The intercept represents the estimated effect size for the reference BMI category (presumably normal weight), which was 0.187 (SE = 0.086, 95% CI: 0.007 to 0.366, t(19) = 2.18, p = 0.042), indicating a small but statistically significant positive effect in this group.

For the overweight, obese I, and obese II BMI category, the coefficient was 0.756 (SE = 0.130, 95% CI: 0.483 to 1.029, t(19) = 5.806, p < 0.001). This suggests that overweight or obese status is associated with an effect size approximately 0.76 units higher than the reference category, representing a substantial and statistically robust increase.

These findings imply that BMI category is an important moderator, with overweight/obese individuals showing markedly larger effect sizes compared to those in the reference group. The strength and precision of the estimates, coupled with the absence of residual heterogeneity in the prior analysis, suggest that BMI category may fully account for the between-study variability observed in the unmoderated model.

DISCUSSION

This meta-regression was informative to show that polycystic ovary syndrome (PCOS) moderates its relationship with circulating levels of kisspeptin based on the body-mass index (BMI) category. Women with PCOS in the overweight/obese range of the BMI scale had significantly higher kisspeptin concentrations than women in the reference (normal weight) group. A coefficient of 0.756 denotes the strong statistically significant increase in Greek points in the levels of kisspeptin in obese women and suggests a possible interaction between adiposity and hypo- pituitary-gonadal (HPG) regulation in PCOS. Raising support to the emerging evidence that metabolic status and especially excess adiposity may cause the potentiation of neuroendocrine changes in PCOS, these findings are consistent with our previous works. The biological possibility of such an outcome lies in the versatile role of kisspeptin in regulatory functions of the reproductive and metabolic processes.[5] Kisspeptin acts via its effect on the release of gonadotropin-releasing hormone (GnRH) to affect the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), both of which are commonly disregulated in PCOS.5 The role of overweight/obese and obesity in reduced insulin sensitivity, hyperinsulinemia, and abnormal leptin signaling and all of them can alter kisspeptin neuron activity has been previously reported.[3] The consequent rise in kisspeptin in the overweight/obese PCOS women could thus represent a compensatory upregulation as a reaction to changed metabolic signals or indeed an escalation of the reproductive endocrine imbalance that derails PCOS.[29] Individually, however, clinically the findings indicate why the inclusion of BMI as a critical stratification factor in assessment of kisspeptin levels is critical in PCOS research and treatment. The increased kisspeptin levels in overweight/obese women with PCOS may also be a predictor of metabolically worsened phenotype that should be treated by both reproductive and metabolic care. Further investigation is needed to establish whether kisspeptin would be a causative variable or merely an effect of the metabolic/reproductive interplay in PCOS and whether specific kisspeptin signaling manipulation may constitute a therapeutic option, especially in overweight/obese individuals.

Building upon the established correlation between adiposity and neuroendocrine dysfunction, the clinical application of these findings offers a transformative perspective on managing the multifaceted challenges of PCOS. For patients facing subfertility, the identification of kisspeptin as a potential biomarker provides a clearer window into the GnRH pulse frequency disturbances that drive chronic anovulation and LH hypersecretion.[5,16] Clinically, this suggests that kisspeptin levels could eventually guide the timing or selection of ovulation induction therapies, moving toward a more precision-based reproductive model. Furthermore, the strong moderation effect of BMI directly addresses metabolic disorders by confirming that overweight/obese status significantly potentiates these hormonal shifts (β = 0.756). This underscores the necessity of integrated care where weight management is not merely an adjunct but a primary intervention to recalibrate the HPG axis. Addressing these underlying metabolic drivers can simultaneously improve body image issues by reducing the physical manifestations of the syndrome, such as weight gain and androgen-related symptoms, which are often exacerbated by the interplay of hyperinsulinemia and kisspeptin signaling. Ultimately, recognizing kisspeptin as a bridge between metabolic status and reproductive health empowers clinicians to move beyond symptom management toward targeted interventions that address the disorder's fundamental pathogenic drivers.

CONCLUSION

This meta-regression analysis indicates that BMI status significantly influences circulating kisspeptin levels in women with PCOS, with overweight/obese individuals exhibiting markedly higher concentrations compared to their normal-weight counterparts. These findings suggest that adiposity may exacerbate neuroendocrine alterations in PCOS, potentially through metabolic–reproductive axis interactions. Recognizing BMI as a moderating factor is essential for both research interpretation and clinical assessment, and future studies should explore whether kisspeptin elevation in overweight/obese PCOS represents a compensatory mechanism or a pathogenic driver amenable to targeted intervention.

CONFLICT OF INTEREST

There are no potential conflicts of interest to disclose.

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