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KISSPEPTIN LEVELS IN WOMEN WITH PCOS: A MARKER FOR HORMONAL DYSREGULATION

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Abstract

Introduction: Polycystic Ovary Syndrome (PCOS) is a prevalent endocrine disorder among women of reproductive age, characterized by hyperandrogenism, oligo/anovulation, and polycystic ovarian morphology. Emerging research has highlighted kisspeptin, a neuropeptide encoded by the *KISS1* gene and acting via the G-protein-coupled receptor GPR54 (KISS1R), as a potential biomarker of hormonal dysregulation in PCOS. The objective of the study is to evaluate serum kisspeptin levels in women with PCOS and their correlation with gonadotropins and other reproductive hormones, assessing its role as a marker of neuroendocrine dysfunction.

Materials and Methods: This comparative study included 180 women (90 PCOS cases and 90 age-matched controls), aged 18–40 years, at a tertiary care center. PCOS diagnosis was based on the Rotterdam criteria. Serum kisspeptin and reproductive hormones, including LH, FSH, testosterone, progesterone, prolactin, SHBG, and DHEAS, were quantified using ELISA and immunoassays. Data were analyzed using SPSS v26.0.

Results: Kisspeptin levels were significantly elevated in PCOS patients (289.0 ± 93.3 pg/mL) compared to controls (240.8 ± 110.6 pg/mL, $p = 0.002$). Positive correlations were observed between kisspeptin and LH (r = 0.564), FSH (r = 0.626), testosterone (r = 0.447), and SHBG (r = 0.497), while

prolactin (r = -0.539) and progesterone (r = -0.553) showed negative correlations ($p < 0.05$ for all). No significant correlation with BMI or thyroid parameters was observed.
Conclusion: Elevated kisspeptin levels and their strong association with key reproductive hormones suggest its integral role in the hypothalamic–pituitary–gonadal (HPG) axis dysregulation characteristic of PCOS. Kisspeptin holds promise as a biomarker for identifying hormonal imbalance, independent of age and metabolic status.

Keywords - Kisspeptin, Polycystic Ovary Syndrome (PCOS), sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulphate (DHEAS).

INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a prevalent and multifaceted endocrine disorder affecting 5–25% of women of reproductive age, characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. [1] [2] The pathogenesis of PCOS is complex, involving a dysregulated hypothalamic–pituitary–gonadal (HPG) axis, insulin resistance, genetic predisposition, and environmental factors. [3] [4] Among the neuroendocrine regulators implicated in the etiology of PCOS, kisspeptin has emerged as a critical peptide hormone influencing reproductive hormone secretion via its action on gonadotropin-releasing hormone (GnRH) neurons. [5] [6]

Kisspeptins, encoded by the *KISS1* gene, act through the G-protein-coupled receptor GPR54 (KISS1R) to stimulate GnRH release, which in turn regulates luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion from the anterior pituitary. [4] [5] [7] This pathway is essential for the initiation and maintenance of reproductive function, and any dysregulation in kisspeptin signaling can result in altered gonadotropin pulsatility, a hallmark of PCOS. [3] [7] Notably, the KNDy (kisspeptin–neurokinin B–dynorphin) neurons in the hypothalamus orchestrate this pulsatile activity, and their dysfunction is increasingly recognized in PCOS pathophysiology. [3] [8]

Recent clinical investigations have reported conflicting observations regarding serum kisspeptin concentrations in women with PCOS. Several studies have demonstrated elevated kisspeptin levels in PCOS patients, suggesting an overactive KISS1 system that contributes to heightened GnRH pulsatility, increased LH secretion, and subsequent hyperandrogenemia. [5] [9] [10] In a Sri Lankan cohort, kisspeptin concentrations were significantly higher in women with PCOS, independent of body mass index (BMI), reinforcing the hypothesis that kisspeptin could serve as an early biomarker for the syndrome, particularly in cases manifesting from adolescence. Similar findings have been documented in Chinese, Korean, and Turkish populations, indicating potential ethnic influences on kisspeptin expression and PCOS phenotype. [10]

Contrasting evidence, however, suggests that kisspeptin levels may vary with obesity and insulin resistance. Daghestani et al. reported no significant difference in kisspeptin concentrations between obese PCOS and non-PCOS women, while noting a negative correlation between kisspeptin and glucose or LH in PCOS subjects. [11] These discrepancies may reflect underlying differences in metabolic status, genetic polymorphisms, or methodological heterogeneity across studies.

Emerging evidence also highlights the complex interplay between kisspeptin and other neuropeptides, such as neurokinin B and γ-aminobutyric acid (GABA), which may modulate GnRH secretion and contribute to the neuroendocrine dysregulation in PCOS. [7][9] Furthermore, insulin resistance—a common feature of PCOS—has been shown to influence kisspeptin signaling, potentially exacerbating hormonal imbalance. [11] [12]

Given its central role in reproductive endocrinology and growing evidence linking it to PCOS pathogenesis, kisspeptin is increasingly regarded as a promising biomarker for hormonal dysregulation in this condition. However, only a limited number of studies have investigated circulating kisspeptin levels in women with PCOS, emphasizing the need for further exploration. The investigation of circulating kisspeptin levels offers valuable insights into the neuroendocrine alterations underlying PCOS and may aid in refining diagnostic and therapeutic strategies tailored to individual pathophysiological profiles. Continued exploration of kisspeptin and its associated pathways is therefore crucial in advancing our understanding of PCOS and enhancing patient care.

MATERIALS AND METHODS

This comparative study was conducted between January 2021 and June 2022 at a Tertiary care centre. The study included 180 women of reproductive age (18–40 years), divided into two groups: 90 women diagnosed with polycystic ovary syndrome (PCOS) based on the Rotterdam criteria (presence of two out of three features: oligo/anovulation, clinical/biochemical hyperandrogenism, and polycystic ovarian morphology) and 90 age-matched healthy controls with regular menstrual cycles and no clinical features of hyperandrogenism. The selection was done using a non-probability convenience sampling method. Ethical approval was obtained from the institutional ethics committee, and informed consent was obtained from all participants before enrolment.

A detailed clinical assessment was performed for all participants, which included recording their medical history, menstrual history, and clinical examination. Anthropometric measurements, including weight, height, and body mass index (BMI), were calculated using standardised protocols. Menstrual regularity was determined based on self-reported cycle lengths over the past year, with irregular cycles defined as intervals outside the normal range of 21–35 days. Exclusion criteria included known thyroid dysfunction, hyperprolactinemia, diabetes mellitus, adrenal disorders, or other chronic systemic illnesses that could influence hormonal parameters.

After an overnight fast, blood samples were collected in the early follicular phase (days 2–5 of the menstrual cycle). The serum was separated and stored at -80°C until analysis. Kisspeptin levels were measured using a specific enzyme-linked immunosorbent assay (ELISA) kit, ensuring high sensitivity and specificity. Hormonal parameters such as luteinising hormone (LH), follicle-stimulating hormone (FSH), oestradiol, testosterone, progesterone, prolactin, thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), sex hormone-binding globulin (SHBG), and dehydroepiandrosterone sulphate (DHEAS) were analysed using commercially available immunoassay kits. Quality control measures were strictly followed to maintain the accuracy and reliability of the results.

The statistical analysis was performed using SPSS software (version 26.0). Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using the independent sample t-test for continuous variables and the chi-square test for categorical variables. Pearson's correlation coefficient was calculated to assess the relationship between serum kisspeptin levels and other clinical or hormonal parameters. A p-value of <0.05 was considered statistically significant.

RESULTS

The demographic and clinical characteristics of the study participants are summarized in Table 1. The mean age distribution between the PCOS group and controls showed no significant difference, with most participants in the 21–30 age range (76.7% vs. 78.9%, p=0.511). Similarly, BMI categories were comparable between the groups, with most women having a BMI ≥ 25 kg/m² (57.8% in PCOS vs. 56.7% in controls, p=0.692). Menstrual irregularities were universal among PCOS patients (100%) compared to 2.2% in controls (p<0.001), highlighting their strong association with the condition.

Table 1: Demographic characteristics

Variable		Cases (n=90)	Controls (n=90)	P value
Age	**<20**	5 (5.6%)	2 (2.2%)	0.511
	21-30	69 (76.7%)	71 (78.9%)	
	31-40	16 (17.7%)	17 (18.9%)	
BMI	**< 18.5**	3 (3.3%)	6 (6.7%)	0.692
	18.5 -22.9	23 (25.6%)	24 (26.7%)	
	23-24.9	12 (13.3%)	9 (10%)	
	>/=25	52 (57.8%)	51 (56.7%)	
Menstrual History	**Regular**	0 (0%)	88 (97.8%)	<0.001
	Irregular	90 (100%)	2 (2.2%)	

Hormonal analysis revealed significant differences between the PCOS and control groups. Serum LH levels were elevated in PCOS patients compared to controls (13.6 ± 6.6 IU/L vs. 7.8 ± 8.3 IU/L, p=0.005), accompanied by an increased LH/FSH ratio (1.76 ± 0.87 vs. 0.69 ± 0.97, p=0.002). Testosterone levels were significantly higher in PCOS patients (33.6 ± 16.0 ng/dL vs. 24.4 ± 14.2 ng/dL, p<0.001), while SHBG levels were lower (65.9 ± 35.0 nmol/L vs. 77.7 ± 45.6 nmol/L, p=0.032). Progesterone levels were also elevated in the PCOS group (10.24 ± 10.25 ng/mL vs. 7.04 ± 8.40 ng/mL, p=0.005). However, oestradiol, prolactin, TSH, T3, T4, and DHEAS levels did not differ significantly between the groups. (Table 2)

Table 2: Biochemical Investigations

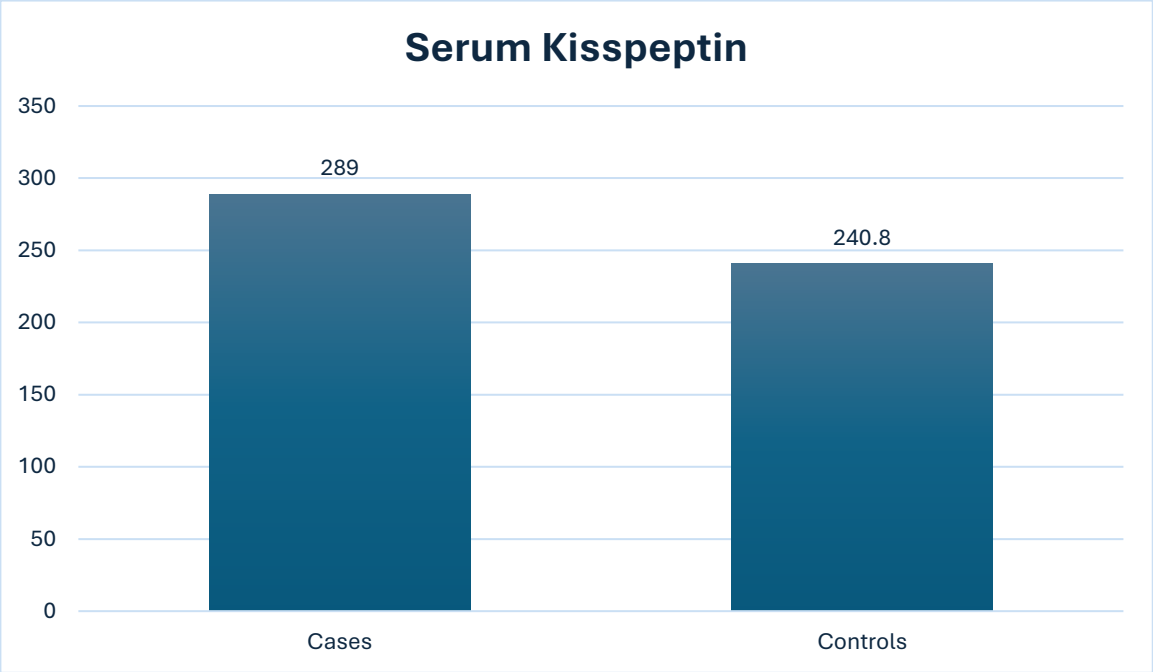
Investigation	Cases (n=90)	Controls (n=90)	P value
LH (IU/L)	13.6 ± 6.6	7.8 ± 8.3	0.005
FSH (IU/L)	6.7 ± 3.0	12.2 ± 1.5	<0.001
LH/FSH Ratio	1.76 ± 0.87	0.69 ± 0.97	0.002
Oestradiol (pg/mL)	65.5 ± 109.0	52.7 ± 53.3	0.316
Prolactin (ng/mL)	23.8 ± 13.4	18.7 ± 15.0	0.025
TSH (µIU/mL)	4.0 ± 5.7	3.8 ± 6.2	0.837
T3 (ng/mL)	2.6 ± 0.8	4.6 ± 11.6	0.102
T4 (µg/dL)	2.5 ± 9.5	1.3 ± 1.0	0.218
Testosterone (ng/dL)	33.6 ± 16.0	24.4 ± 14.2	<0.001
Progesterone (ng/mL)	10.24 ± 10.25	7.04 ± 8.40	0.005
SHBG (nmol/L)	65.9 ± 35.0	77.7 ± 45.6	0.032
DHEAS (µg/mL)	1.0 ± 0.5	0.9 ± 0.6	0.486

Serum kisspeptin levels were significantly higher in PCOS patients than in controls (289.0 ± 93.3 pg/mL vs. 240.8 ± 110.6 pg/mL, p=0.002). (Figure 1) Kisspeptin levels demonstrated a positive correlation with LH (r = 0.564, p = 0.023), FSH (r = 0.626, p = 0.017), testosterone (r = 0.447, p = 0.047), and SHBG (r = 0.497, p = 0.039), while significant negative correlations were noted for prolactin (r = -0.539, p = 0.041) and progesterone (r = -0.553, p = 0.025). In contrast, the control group showed no significant correlations. Also, no significant correlations were observed between kisspeptin and BMI, age, Oestradiol, TSH, T3, T4 and DHEAS in either group. (Table 3)

Table 3: Correlation analysis of Kisspeptin between cases and controls

Parameter	Cases		Controls	
	Pearsons Correlation	P value	Pearsons Correlation	P value
Age	0.057	0.591	-0.136	0.202
BMI	-0.015	0.885	-0.126	0.238
LH	0.564	0.023	0.152	0.116
FSH	0.626	0.017	0.143	0.178
Oestradiol	0.216	0.183	0.094	0.380
Prolactin	-0.539	0.041	-0.079	0.560
TSH	-0.201	0.057	-0.135	0.208
T3	0.058	0.584	0.040	0.710
T4	0.073	0.495	0.063	0.558
Testosterone	0.447	0.047	0.197	0.965
Progesterone	-0.553	0.025	-0.059	0.588
SHBG	0.497	0.039	0.105	0.896
DHEAS	0.083	0.476	0.136	0.201

Figure 1: Bar chart showing Serum Kisspeptin levels in cases and controls



DISCUSSION

The present study investigated the role of serum kisspeptin as a biomarker of hormonal dysregulation in women with PCOS and found significantly elevated kisspeptin levels in PCOS patients compared to controls. This increase was accompanied by elevated LH, testosterone, progesterone, and LH/FSH ratios, while SHBG levels were decreased. Notably, kisspeptin levels in PCOS patients positively correlated with LH, FSH, testosterone, and SHBG, and negatively with prolactin and progesterone. These findings reinforce the hypothesis that kisspeptin is integrally involved in the neuroendocrine dysregulation that characterizes PCOS.

Comparable to these findings, Umayal et al. (2018) [10] also reported significantly elevated serum kisspeptin levels in South Asian women with PCOS, independent of BMI. Their results highlighted that kisspeptin might serve as a useful early diagnostic marker, especially in adolescent-onset PCOS. The present study aligns with this, as elevated kisspeptin levels were observed in a similarly young population, most aged between 21–30 years.

Consistent with the present study, Tang et al. (2019) [5] reported increased serum kisspeptin levels in PCOS patients, supporting its role in the overstimulation of GnRH neurons, thereby contributing to excessive LH secretion and subsequent hyperandrogenism. The significant correlation between kisspeptin and LH, FSH, and testosterone in the current data further strengthens this mechanistic pathway. However, the negative correlation with prolactin and progesterone may reflect complex feedback loops within the hypothalamic–pituitary–gonadal (HPG) axis, where elevated kisspeptin could suppress prolactin secretion or vice versa, as documented by Szeliga et al. (2022) who highlighted that hyperactivity of kisspeptin neurons can disrupt the normal feedback inhibition required for menstrual regulation.

Interestingly, not all studies have agreed on the elevation of kisspeptin in PCOS. Cheng et al. (2025) [9] found lower kisspeptin and neurokinin B levels in PCOS patients, particularly among those with metabolic disturbances. They proposed that GABA-mediated inhibition of kisspeptin neurons may contribute to this suppression, especially in metabolically unhealthy PCOS phenotypes. This contrasts with the present findings, where kisspeptin showed no significant association with BMI, suggesting that in this population, kisspeptin expression may be independent of adiposity and metabolic status.

Daghestani et al. (2021) [11] observed no overall difference in kisspeptin levels between obese PCOS and obese non-PCOS women but reported altered correlations with LH and glucose. The negative association with glucose and lack of correlation with BMI support the view that kisspeptin regulation

in PCOS may depend more on neuroendocrine than metabolic mechanisms. Our findings corroborate this interpretation, given the absence of any significant kisspeptin–BMI correlation.

In addition, the current study revealed a significant increase in serum LH and LH/FSH ratio in PCOS patients, a classic endocrine hallmark. The positive association of kisspeptin with these hormones reinforces its upstream regulatory role. This agrees with Dong et al. (2023), [3] who elaborated on the role of KNDy neurons—comprising kisspeptin, neurokinin B, and dynorphin—in modulating GnRH pulse frequency. They proposed that an upregulated kisspeptin signaling pathway may explain the abnormal LH hypersecretion seen in PCOS.

Furthermore, Emanuel et al. (2022) [4] emphasized the centrality of kisspeptin in initiating reproductive hormone secretion and discussed how its dysregulation could lead to PCOS-related ovulatory dysfunction and subfertility. Their insights support the current study's correlation of elevated kisspeptin with key reproductive hormones. Interestingly, Hussein et al. (2024) [12] discussed the dual role of kisspeptin in regulating both reproductive and metabolic functions, suggesting that insulin resistance may modulate kisspeptin secretion. In contrast, the present study found no association between kisspeptin and BMI, suggesting population-specific variability or the influence of other confounding factors such as diet, ethnicity, or genetic polymorphisms.

Roy P et al. (2023) [8] and Hajam et al. (2024) [1] also described the neuroendocrine basis of PCOS, including the role of kisspeptin in modulating GnRH and LH secretion, aligning with the present findings. Both studies emphasized the need for standardized kisspeptin assays and further large-scale research to clarify its diagnostic and prognostic potential. Lastly, the review by Kokori et al. (2024) [6] stressed the diagnostic promise of serum kisspeptin while acknowledging variability in results due to methodological differences, assay sensitivity, and population heterogeneity. They advocated for standardized protocols in kisspeptin quantification and urged exploration into genetic polymorphisms that may underlie its differential expression in PCOS patients.

The present study contributes important evidence supporting the role of serum kisspeptin as a marker of hormonal dysregulation in PCOS. The elevated levels and their significant associations with key reproductive hormones in affected individuals reinforce the peptide's central role in the pathophysiology of PCOS. While results are largely concordant with previous literature, discrepancies underscore the heterogeneity of PCOS and the potential influence of metabolic, genetic, and environmental factors on kisspeptin expression.

This study is limited by its cross-sectional design, single-center setting, and lack of metabolic parameter assessment such as insulin resistance. Kisspeptin was measured at a single time point without accounting for menstrual cycle variation. Additionally, PCOS phenotypes were not stratified, and other neuropeptides like neurokinin B or GABA were not evaluated. These factors may affect the generalizability and depth of mechanistic insights. Future multicentric studies with standardized methodologies and subgroup analyses based on metabolic phenotype are warranted to clarify the diagnostic and therapeutic implications of kisspeptin in PCOS.

CONCLUSION

This study demonstrates that serum kisspeptin levels are significantly elevated in women with PCOS and show strong positive correlations with LH, FSH, testosterone, and SHBG, alongside negative associations with prolactin and progesterone. These findings highlight kisspeptin’s pivotal role in the neuroendocrine dysregulation characteristic of PCOS, independent of age and BMI. Given its consistent association with key reproductive hormones, kisspeptin emerges as a promising biomarker for identifying hormonal imbalance in PCOS. Future longitudinal and multi-center studies incorporating metabolic parameters and neuropeptide profiling are warranted to validate its diagnostic and therapeutic potential.

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