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The Kallistatin-Zearalenone Axis: A Novel Perspective On Metabolic And Reproductive Health In PCOS-Related Infertility

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Abstract:
This study investigated the impact of infertility types on metabolic indices in Polycystic Ovary Syndrome (PCOS) patients, focusing on the roles of kallistatin and zearalenone (ZEN). A comparative analysis was conducted among women with Type 1 infertility, Type 2 infertility, an unmarried PCOS group, and healthy controls.
A cross-sectional study recruiting 138 women from the Obstetrics and Gynecology Hospital in Karbala and Baghdad Teaching Hospital (Medical City). Included 98 patients diagnosed with Polycystic Ovary Syndrome (PCOS) and 40 apparently healthy women who served as a control group.
PCOS was diagnosis based on the 2012 Rotterdam consensus criteria: presence of at least two of three features: clinical/biochemical hyperandrogenism, oligo- or amenorrhea, and/or polycystic ovarian morphology (PCOM) via ultrasonography. Elisa system was used for the detection of Kallistatin level. Zearalenone levels were measured qualitatively by Thin layer chromatography and quantitatively by high-performance liquid chromatography analyses demonstrated significant variations in kallistatin and ZEN levels. Kallistatin, an anti-inflammatory serine protease inhibitor, was significantly lower in all PCOS groups compared to healthy controls, with the lowest concentration observed in the unmarried PCOS group. Among infertile women, Type 2 patients had slightly lower kallistatin levels than Type 1 patients. Conversely, ZEN, a mycoestrogen, was significantly elevated in the unmarried PCOS group, while Type 1 and Type 2 infertility groups had similar ZEN levels, and the control group had the lowest.
The elevated ZEN levels, especially in the unmarried group, raise concerns about the contribution of environmental endocrine disruptors to PCOS pathophysiology. Future research should further explore kallistatin as a diagnostic/prognostic marker and investigate strategies to mitigate dietary ZEN exposure to improve reproductive outcomes in PCOS.
Keywords: *Polycystic Ovary Syndrome (PCOS), Metabolic Indices, Kallistatin, Zearalenone (ZEN)*

INTRODUCTION:

Polycystic Ovary Syndrome (PCOS) is one of the most prevalent endocrine disorders affecting women of reproductive age and represents a leading cause of anovulatory infertility worldwide (1). Beyond its reproductive consequences, PCOS also carries a significant metabolic burden, contributing to insulin resistance, hyperandrogenism, and systemic inflammation, all of which further complicate fertility outcomes (2).

While the hormonal and metabolic underpinnings of PCOS-related infertility have been widely studied, growing attention is now being directed toward the role of environmental and molecular factors that may exacerbate reproductive dysfunction. One such factor is Zearalenone (ZEN), an estrogenic mycotoxin that can interfere with the endocrine system and potentially worsen hormonal imbalances in susceptible individuals (3). Chronic exposure to ZEN has been associated with reproductive toxicity in animal models, raising concerns about its role in human reproductive health, particularly among women already predisposed to ovulatory dysfunction (4) .

In parallel, Kallistatin, a multifunctional serine protease inhibitor with known anti-inflammatory and anti-fibrotic properties, has emerged as a potential modulator of ovarian function. Alterations in kallistatin levels may influence ovarian angiogenesis, fibrosis, and local inflammatory responses—all of which are relevant to PCOS pathophysiology and its impact on fertility (5).

Given these insights, exploring the interaction between environmental toxins like ZEN and endogenous regulators such as Kallistatin could provide a deeper understanding of the mechanisms driving infertility in PCOS. This study aims to investigate these associations and assess their potential value as biomarkers or therapeutic targets in affected women.

Polycystic Ovary Syndrome (PCOS) is a complex endocrine-metabolic disorder characterized by a constellation of reproductive, hormonal, and metabolic abnormalities. It is clinically diagnosed based on the Rotterdam criteria, which require the presence of at least two of the following three features: oligo/anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology (6). PCOS is phenotypically diverse and is commonly categorized into four phenotypes (A–D), with phenotype A (hyperandrogenism, anovulation, and polycystic ovaries) being the most severe in terms of both metabolic and reproductive disturbances.

The impact of PCOS on fertility is profound, as chronic anovulation impairs the cyclical release of mature oocytes required for successful conception. This anovulatory state is largely driven by hormonal dysregulation, including elevated luteinizing hormone (LH), altered LH:FSH ratio, and excess ovarian androgen production (1). Additionally, insulin resistance—a common metabolic feature in PCOS—further amplifies androgen production and exacerbates reproductive dysfunction. The resulting hormonal environment disrupts follicular growth, impairs oocyte maturation, and reduces endometrial receptivity, all of which contribute to infertility (2).

In addition to these well-established mechanisms, recent research has highlighted the possible contribution of environmental endocrine disruptors, such as Zearalenone (ZEN), to the pathophysiology of infertility in PCOS. ZEN is a non-steroidal mycotoxin produced by Fusarium species and is structurally similar to estradiol. Due to its affinity for estrogen receptors, ZEN can mimic estrogenic activity and interfere with the hypothalamic–pituitary–gonadal (HPG) axis (3). Chronic exposure to ZEN, even at low doses, has been associated with ovarian dysfunction, altered estrous cycles, and reduced fertility in animal models (4). In PCOS patients, who already exhibit hormonal imbalance, ZEN may further worsen the endocrine disruption and contribute to anovulation and reduced reproductive capacity (7).

Another emerging factor of interest in the context of PCOS-related infertility is Kallistatin, a member of the serine protease inhibitor (SERPIN) family. Kallistatin is known for its vasoprotective, anti-inflammatory, and anti-fibrotic functions. It has been implicated in the regulation of angiogenesis, oxidative stress, and tissue remodeling (5). In the ovaries, these processes are critical for normal follicular development and ovulation. Studies have suggested that Kallistatin may exert protective effects against the pathological changes seen in polycystic ovaries, such as excessive stromal fibrosis and abnormal vascularization. Reduced kallistatin levels might thus contribute to the disturbed intra-ovarian environment observed in PCOS, ultimately affecting oocyte quality and fertility outcomes.

Together, these findings underscore the multifactorial nature of infertility in PCOS and point to the potential role of both external (e.g., ZEN) and internal (e.g., Kallistatin) modulators in exacerbating reproductive dysfunction. Investigating the levels of these markers and their association with ovulatory status may provide novel insights into the pathophysiology of PCOS and open new avenues for diagnosis and therapeutic intervention. This study aimed to investigate the levels of Zearalenone and Kallistatin among PCOS patients groups based on types of infertility.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

A cross-sectional study was conducted between September 2024 and July 2025 in Iraq. The participants were recruited from the Obstetrics and Gynecology Hospital in Karbala and the Baghdad Teaching Hospital (Medical City). The study aimed to investigate the serum levels of Zearalenone and Kallistatin among women diagnosed with Polycystic Ovary Syndrome (PCOS) and explore their relationship with reproductive hormones and metabolic parameters.

2.2 Ethical Consideration

The study was approved by the Ethical Committee of the College of Medicine, University of Karbala. The ethical approval letter NO: 24-59 Date :2025/7/10

All participants provided informed consent prior to enrollment. Privacy and confidentiality were maintained throughout the study.

2.3 Study Participants

A total of 98 women aged between 18 and 44 years, all diagnosed with PCOS based on the 2012 revised Rotterdam criteria, were included. The diagnosis required at least two of the following features: clinical/biochemical hyperandrogenism, oligo- or anovulation, and/or polycystic ovarian morphology (PCOM) by ultrasound.

2.4 Inclusion and Exclusion Criteria

Women were excluded if they were pregnant, breastfeeding, or had other endocrine disorders such as thyroid dysfunction, hyperprolactinemia, or congenital adrenal hyperplasia. Additional exclusions included diabetes mellitus, cardiovascular disease, autoimmune conditions, hepatic or renal dysfunction, or current corticosteroid therapy. These criteria aimed to minimize potential confounding factors.

2.5 Sample Collection and Processing

Venous blood samples were collected in the early follicular phase of the menstrual cycle, after overnight fasting. Serum was separated by centrifugation and stored at –20°C until biochemical analysis.

2.6 Zearalenone Detection

Zearalenone (ZEN) in serum was first extracted and identified qualitatively using Thin Layer Chromatography (TLC), followed by quantitative analysis using High Performance Liquid Chromatography (HPLC).

2.7 Kallistatin Measurement

Serum kallistatin concentrations were determined using the Elabscience® Human SERPINA4 (Kallistatin) ELISA Kit, following the manufacturer's instructions. Absorbance was read at 450 nm using a microplate reader.

2.8 Anthropometric and Metabolic Measurements

Serum lipid concentration ((total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein (LDL)and triglycerides (TG)) fully automatic chemistry analyzer (SMART-120, Geno TEK, United States of America). Anthropometric indices including body mass index (BMI), waist-to-hip ratio (WHR), body adiposity index (BAI), and lipid accumulation product (LAP) were recorded. Basal metabolic rate (BMR) was also estimated. Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR).

2.9 Statistical Analysis

Data analysis was performed using SPSS version 26. Descriptive statistics were expressed as mean ± SD or median (min–max), depending on distribution. Inter-group comparisons were conducted using appropriate statistical tests such as ANOVA or Kruskal–Wallis, followed by post hoc analysis. A p-value < 0.05 was considered statistically significant.

RESULTS:

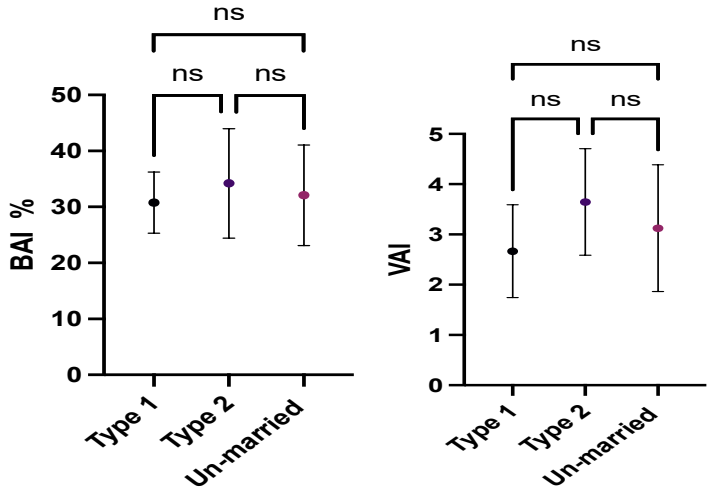
To assess the impact of infertility types on metabolic and molecular profiles in PCOS patients, Tables 1 provide a comparative analysis between women with Type 1 infertility (anovulatory without tubal or male factor), Type 2 infertility (with tubal or male factor), and an unmarried group.

Metabolic Parameters: As shown in Table 1 & Figure 1, Body Adiposity Index (BAI) was similar across all groups, with medians of 30%, 33%, and 32% in Type 1, Type 2, and unmarried patients respectively. However, significant differences were noted in other metabolic indices. The Visceral Adiposity Index (VAI) was highest in the Type 2 infertility group (3.4), followed by the unmarried (2.9) and Type 1 (2.4) groups. Similarly, the Lipid Accumulation Product (LAP) was markedly elevated in Type 2 patients (median: 94), indicating greater lipid burden compared to Type 1 (67) and unmarried women (76). Basal Metabolic Rate (BMR) also showed a similar trend, with the highest median BMR in Type 2 patients (1478 kcal/day) versus 1390 kcal/day in Type 1 and 1422 kcal/day in unmarried patients.

Table 1. Biochemical evaluation of metabolic incised (Median (mini-max)) among PCOS groups based on types of infertility.

	Infertility Type 1	*Infertility Type 2*	*Un-married*
BAI	*30 (25-53*	*33 (19-70*	*32 (19-53*
VAI	*2.4 (1.9-4*	*3.4 (2.3-5.4*	*2.9 (1.7-4.5*
LAP	*67 (37-348*	*94 (10-583*	*76 (9.1-406*
BMR	*1390 (1192-1898*	*1478 (1145-1894*	*1422 (1232-1904*

*body adiposity index (BAI), visceral adiposity index (VAI), lipid accumulation product (LAP), and basal metabolic rate (BMR)



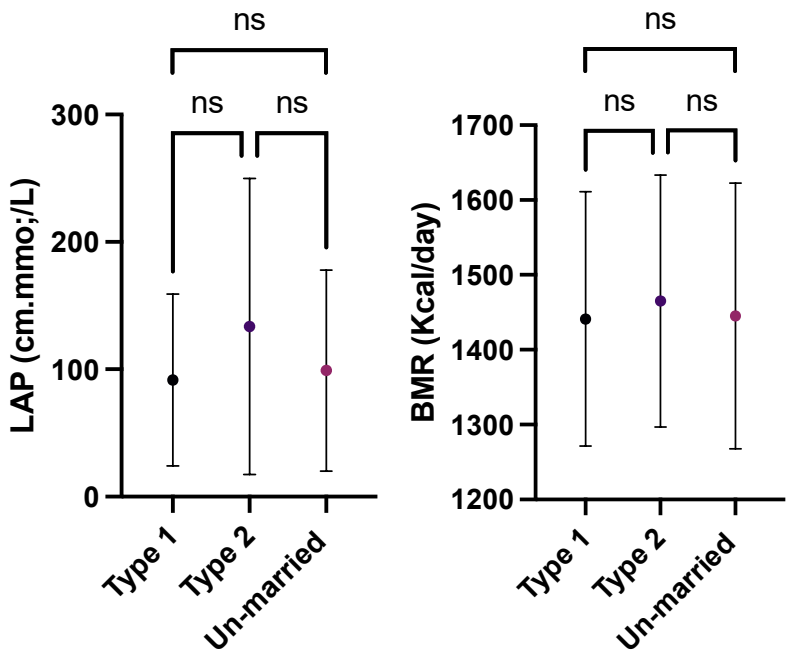


Figure 1. The distribution of evaluation metabolic incised among PCOS patients groups based on types of infertility (Post Hoc ANOVA test was *: significant at p ≤ 0.05, **: significant at p ≤ 0.01, ***: significant at p ≤ 0.001, *: significant at p ≤ 0.0001)***

Kallistatin and Zearalenone Levels

Table 2 presents molecular findings, specifically focusing on kallistatin and zearalenone (ZEN) levels. Kallistatin, a serine protease inhibitor with anti-inflammatory functions, was significantly lower in PCOS patients compared to healthy controls. Among infertile women, Type 1 patients had a median level of 42 ng/mL (range: 4.2–271), while Type 2 patients had a slightly lower median of 37 ng/mL (range: 1.4–247). The unmarried group exhibited the most pronounced deficiency, with a median of 9.6 ng/mL (range: 2.0–68). For comparison, the healthy control group had a median kallistatin level of 66 ng/mL (range: 16–342), suggesting a potential role of kallistatin in reproductive dysfunction.

Table 2. Mean level of Kallistatin and Zearalenone (Median (mini-max)) among PCOS patients groups based on types of infertility

	Infertility Type 1	*Infertility Type 2*	*Un-married*	*Healthy Control*
Kallistatin	*42 (4.2-271)*	*37 (1.4-247)*	*9.6 (2.0-68)*	*66 (16-342)*
Zearalenone ng/L	*4.8 (2.7-11)*	*4.8 (2.1-12)*	*7.2 (3.3-16)*	*4.2 (2.1-8.2)*

In terms of Zearalenone (ZEN), a mycoestrogen known to disrupt hormonal balance, levels were relatively similar in Type 1 and Type 2 infertility groups (both with a median of 4.8 ng/L). However, the unmarried group exhibited significantly elevated ZEN levels (median: 7.2 ng/L), while the control group had the lowest (4.2 ng/L). These results highlight the potential involvement of environmental endocrine disruptors in PCOS-related infertility, especially among women with less defined clinical categories.

Figure 2 complements these observations, showing the distribution patterns of kallistatin and ZEN across the infertility-based subgroups. The graphical data confirmed the trend of decreasing kallistatin and increasing ZEN levels in patients with infertility and PCOS.

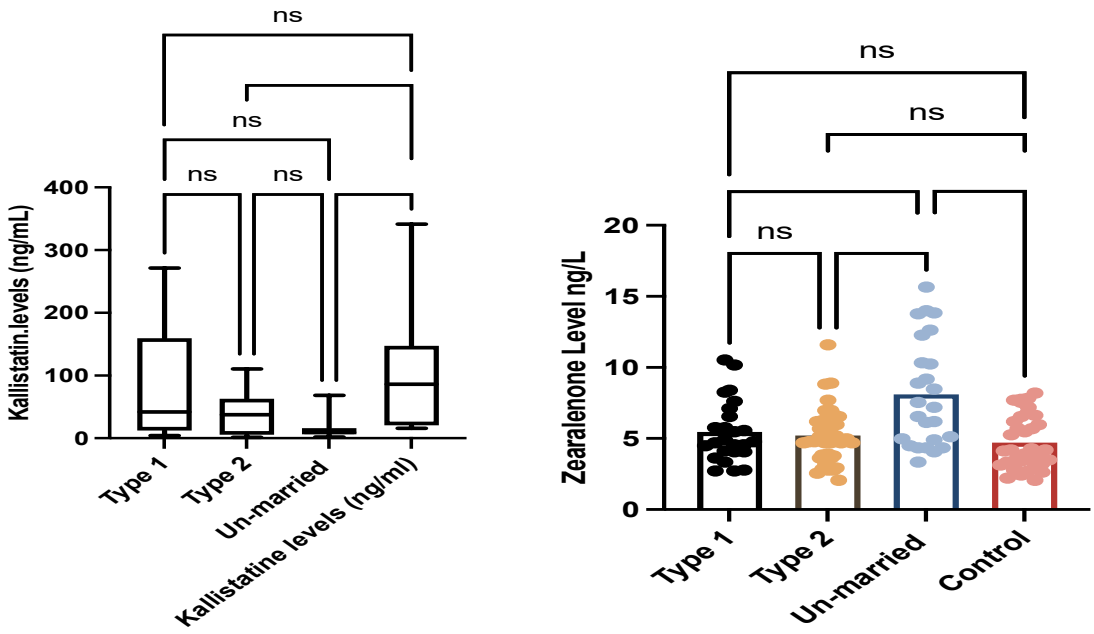


Figure 2. The distribution of serum level of Kallistatin and Zearalenone among PCOS patients groups based on types of infertility (Post Hoc ANOVA test was *: significant at p ≤ 0.05, **: significant at p ≤ 0.01, ***: significant at p ≤ 0.001, *: significant at p ≤ 0.0001)***

Diagnostic performance of Kallistatin and Zearalenone among PCOS patients groups based on types of infertility compared to healthy controls

The diagnostic performance of Zearalenone for distinguishing PCOS patients with Infertility Type I was evaluated using a Receiver Operating Characteristic (ROC) curve. The Area Under the Curve (AUC) for Zearalenone was determined to be 0.61. At an optimal cut-off value of > 4.37 ng/L, Zearalenone demonstrated a sensitivity of 68% and a specificity of 58.3%. However, the statistical significance for this discriminatory power was not reached, as indicated by a (P-value of >0.05). similarly, Kallistatin, the Area Under the Curve (AUC) was 0.60. At an optimal cut-off value of < 94.5 ng/mL, Kallistatin demonstrated a sensitivity of 67% and a specificity of 50%. Both Kallistatin and Zearalenone demonstrated limited diagnostic utility for distinguishing PCOS patients with Infertility Type I, with neither biomarker achieving statistical significance. Zearalenone exhibited marginally better performance metrics (higher AUC, sensitivity, and specificity) compared to Kallistatin, although both were statistically non-significant in this context.

The diagnostic performance of Zearalenone for distinguishing PCOS patients with Infertility Type II was further evaluated using a Receiver Operating Characteristic (ROC) curve. The Area Under the Curve (AUC) for Zearalenone was found to be 0.57. At an optimal cut-off value of > 4.48 ng/L, Zearalenone demonstrated a sensitivity of 68% and a specificity of 58.3%. These findings suggest that Zearalenone has limited utility as a diagnostic marker for Infertility Type II in PCOS patients.

Kallistatin demonstrated good discriminatory power with an (AUC) of 0.75. At an optimal cut-off value of < 48.5 ng/mL, Kallistatin yielded a sensitivity of 71% and a specificity of 65%. Notably, the diagnostic utility of Kallistatin was statistically significant, as indicated by a P-value of 0.007. These findings suggest that Kallistatin holds promise as a diagnostic biomarker for Infertility Type II in PCOS patients. Kallistatin appears to be a more valuable diagnostic biomarker for PCOS patients with Infertility Type II compared to Infertility

Type I, and also significantly outperforms Zearalenone in this specific context. Neither Zearalenone nor Kallistatin show significant diagnostic promise for Infertility Type I in PCOS patients based on these results. Zearalenone demonstrated much better discriminatory power among PCOS patients/ *un-married grou*p with an Area Under the Curve (AUC) of 0.79. At an optimal cut-off value of > 4.305 ng/L, Zearalenone yielded a high sensitivity of 92% and a specificity of 58.3%. Notably, the diagnostic utility of Zearalenone in this group was statistically significant, as indicated by a P-value of 0.001. These findings shown that Zearalenone holds promise as a diagnostic biomarker for distinguishing PCOS patients within the unmarried population. Also, Kallistatin demonstrated the strongest discriminatory power across all analyses in the unmarried PCOS group. It achieved an excellent AUC of 0.91, indicating very high diagnostic accuracy. At a cut-off of < 31.5 ng/mL, it showed 87.5% sensitivity and 70% specificity. This finding was highly statistically significant (P < 0.0001).
A clear pattern emerges from these results regarding the utility of Zearalenone and Kallistatin in different PCOS subgroups. In Infertility Types (I & II), Both Zearalenone and Kallistatin show limited or no statistically significant diagnostic utility for Infertility Type I. However, for Infertility Type II, Kallistatin emerges as a statistically significant and promising biomarker (AUC 0.75, P=0.007), whereas Zearalenone's performance remains non-significant.
For unmarried PCOS group , Both biomarkers show significantly enhanced diagnostic capabilities compared to the infertility types. Kallistatin, in particular, demonstrates exceptional discriminatory power (AUC 0.91, P<0.0001), surpassing Zearalenone's strong performance (AUC 0.79, P=0.001).

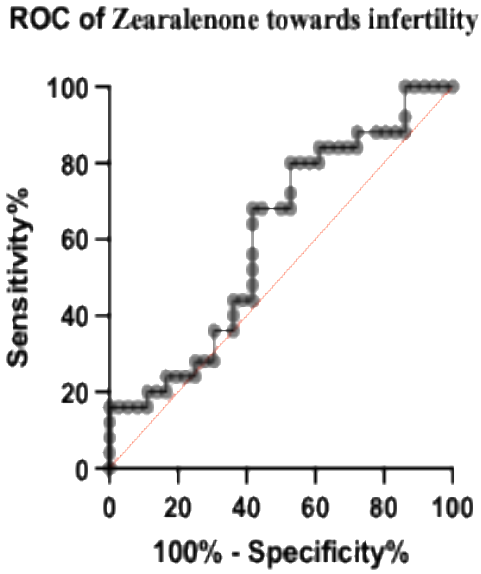


Figure 13. ROC curve of *Zearalenone* PCOS patients/ ***Infertility type I*** (Total and Stratification levels). (*Zearalenone*: AUC 0.61, 68% sensitivity, 58.3% specificity, cut-off > 4.37 ng/L, *P* value was 0.1

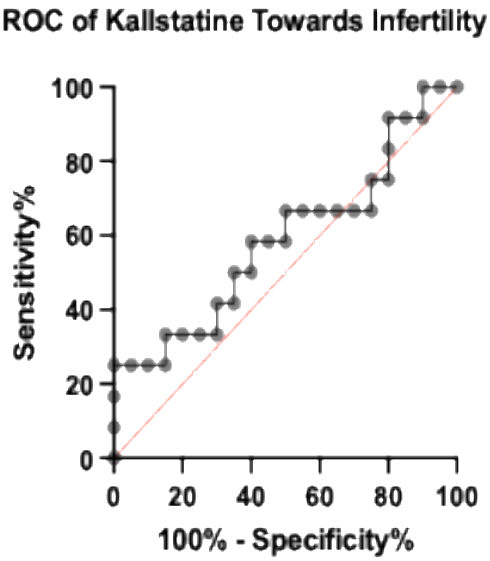


Figure : ROC curve of Kallistatin PCOS patients/ ***Infertility type I*** (Total and Stratification levels). (Kallistatin: AUC 0.6, 67% sensitivity, 50% specificity, cut-off <94.5 ng/mL, *P* value was 0.4

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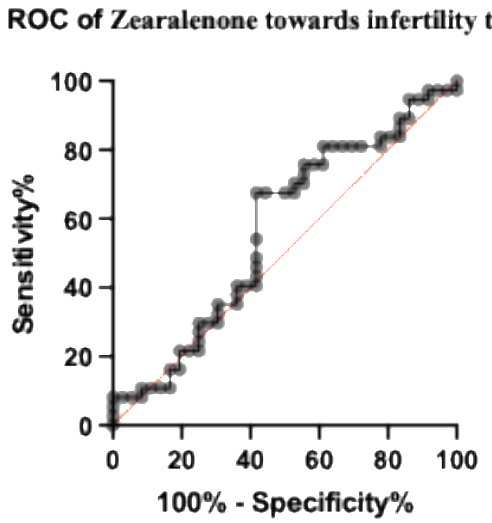

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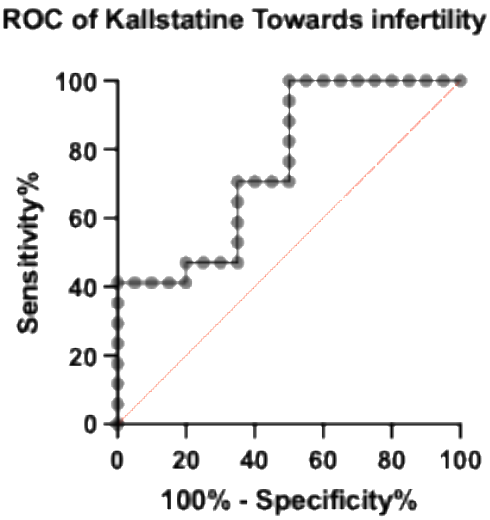

Figure : ROC curve of Kallistatin PCOS patients/ ***Infertility type II*** (Total and Stratification levels). (Kallistatin: AUC 0.75, 71% sensitivity, 65% specificity, cut-off <48.5 ng/mL, *P* value was 0.007

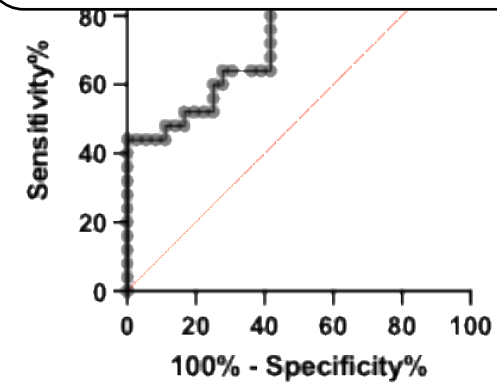

Figure 13. ROC curve of *Zearalenone* PCOS patients/ ***un-married grou***p (Total and Stratification levels). (*Zearalenone*: AUC 0.79, 92% sensitivity, 58.3% specificity, cut-off > 4.305 ng/L, *P* value was 0.001

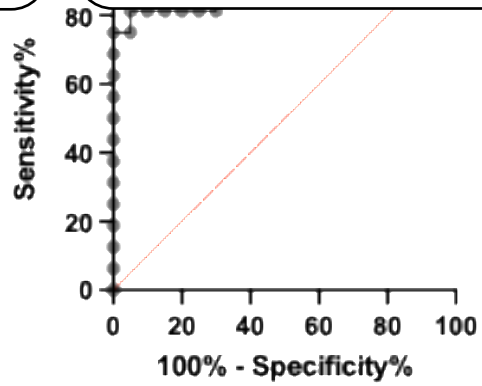

Figure : ROC curve of Kallistatin PCOS patients/ ***un-married group*** (Total and Stratification levels). (Kallistatin: AUC 0.91, 87.5% sensitivity, 70% specificity, cut-off <31.5 ng/mL, *P* value was <0.0001

DISCUSSION

This study explored the metabolic underpinnings of infertility in women with PCOS, focusing particularly on the roles of Zearalenone (ZEN) and kallistatin. The data revealed key differences between patients with type 1 and type 2 infertility, with implications for understanding the interplay between environmental and endogenous factors in reproductive dysfunction. Analysis of the metabolic indices revealed significant differences between PCOS patients, depending on the type of infertility and marital status. While body adiposity index (BAI) values were relatively constant between groups (ranging from 30 to 33), more marked differences were observed in visceral adiposity index (VAI) and lipid accumulation product (LAP). Patients

with type II infertility had the highest VAI (3.4) and LAP (94), indicating a greater burden of visceral adiposity and fat accumulation compared to patients with type I infertility and single patients.

These results reflect a better understanding of the metabolic complexity of PCOS. According to Wang et al. (8) visceral fat plays a critical role in inducing insulin resistance and pro-inflammatory states, two factors that exacerbate reproductive and metabolic dysfunction in PCOS.

LAP, another lipid-related indicator of metabolic risk, was also more pronounced in the type 2 infertility group. LAP is increasingly recognized as a reliable indicator of cardiometabolic risk in PCOS patients, as demonstrated by (9), who observed a strong association between elevated LAP and increased insulin resistance, particularly in women with oligo-/anovulatory pathologies.

In contrast, basal metabolic rate (BMR) varied slightly between groups, with the type 2 infertility group having the highest mean (1,478 kcal/day). BMR is influenced by multiple factors, including lean body mass and age.

Due to the marked differences in adiposity and metabolic parameters in PCOS patients, the subsequent analysis in Table 5 focuses on two novel molecular factors: kallistatin and zearalenone. Studying the levels of these factors may provide a deeper understanding of the interaction between autoanti-inflammatory proteins and environmental estrogenic toxins in the pathophysiology of PCOS.

The data shown significant variation in kalistatin and zearalenone (ZEN) levels across PCOS subgroups. Notably, the control group had the highest mean kalistatin level (66 ng/ml), while the lowest concentration was observed in the unmarried PCOS group (mean: 9.6 ng/ml). In Type 1 infertility patients, the mean kalistatin level was higher (42 ng/ml) than in Type 2 infertility patients (37 ng/ml).

This pattern is consistent with the findings of Zhao et al. (10), who suggested that decreased kalistatin may be associated with systemic inflammation and endothelial dysfunction in PCOS, especially in women with more advanced metabolic disorders. The significantly lower levels in the unmarried group may indicate a distinct pathological course, perhaps reflecting increased oxidative stress or chronic inflammation not directly related to infertility.

In addition, these results are also consistent with the study by Chen et al. (11), who reported that kallistatin plays a vascular protective and anti-inflammatory role, and that its deficiency may serve as a biomarker of endocrine and metabolic disturbances in PCOS, particularly in phenotypes with marked hormonal imbalance.

For zearalenone, a mycotoxin with known estrogenic activity, the highest mean level was again observed in the unmarried group (7.2 ng/L), followed by the unmarried group (4.8 ng/L), while the control group recorded the lowest level (4.2 ng/L). These findings raise concerns about the potential contribution of environmental endocrine disruptors to the pathophysiology of PCOS, as emphasized by Rashid et al (12).

ZEN can therefore mimic estrogen and bind to its receptors, potentially disrupting the hypothalamic-pituitary-gonadal axis. Wang et al. (13) highlighted that chronic exposure to ZEN can exacerbate hormonal imbalances and reproductive function, particularly in vulnerable populations. The current findings reinforce this hypothesis, particularly with higher ZEN levels in the group with the lowest kalistatin levels, suggesting a potential synergistic imbalance affecting endocrine and metabolic stability.

In overview, these findings suggest a dual influence of endogenous (inflammatory/antiprotease imbalance via kalistatin) and exogenous (mycotoxin exposure) mechanisms in the onset of PCOS symptoms. The variability between groups highlights the need for individualized assessment, especially in women with atypical symptoms, such as those who are single or with undiagnosed infertility.

Conclusion

This study highlights the significant differences in metabolic profiles between infertile PCOS patients, emphasizing the dual role of endogenous and exogenous factors in reproductive dysfunction. Type 1 infertility was associated with classic hyperandrogenic features, while type 2 infertility showed a stronger metabolic burden and elevated prolactin levels.

Kallistatin emerged as a promising biomarker, with significantly lower levels in all PCOS groups—particularly in those with more severe metabolic profiles—supporting its utility in reflecting inflammatory status and

disease severity. Conversely, ZEN levels were elevated in specific subgroups, suggesting its role as an environmental contributor to endocrine and reproductive disruption.

These findings underscore the importance of incorporating both clinical phenotyping and molecular profiling in PCOS management. Future research should further explore kallistatin as a diagnostic or prognostic marker and investigate strategies to mitigate dietary exposure to ZEN to improve reproductive outcomes.

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