IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 25, Issue 6 Ser. 5 (June. 2026), PP 65-72
www.iosrjournals.org

Association of Pregnancy-Associated Plasma Protein-A (PAPP-A) with Insulin Resistance, Interleukin-18, Gonadotropins, and Anti-Müllerian Hormone in Women with Polycystic Ovary Syndrome: A Cross-Sectional Analytical Study

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Abstract
Background
Polycystic ovary syndrome (PCOS) is a common endocrine-metabolic disorder characterized by hyperandrogenism, ovulatory dysfunction, insulin resistance, and chronic low-grade inflammation. Pregnancy-associated plasma protein-A (PAPP-A) has been implicated in insulin-like growth factor regulation and metabolic dysfunction; however, its role in PCOS remains incompletely understood.
Objectives
To estimate serum levels of PAPP-A, fasting blood sugar (FBS), fasting insulin, interleukin-18 (IL-18), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) in women with PCOS; to calculate insulin resistance using HOMA-IR; and to determine the correlation of PAPP-A with LH/FSH ratio, HOMA-IR, anti-Müllerian hormone (AMH), and IL-18.
Methods
A cross-sectional analytical study was conducted among 60 women diagnosed with PCOS and 60 age-matched healthy controls. Serum PAPP-A, IL-18, insulin, LH, FSH, and AMH levels were estimated by ELISA and chemiluminescence assays. Insulin resistance was assessed using HOMA-IR.
Results
Women with PCOS demonstrated significantly higher serum PAPP-A (5.8 ± 1.7 vs. 3.4 ± 1.1 ng/mL, $p<0.001$), IL-18 (356 ± 82 vs. 198 ± 56 pg/mL, $p<0.001$), fasting insulin (18.9 ± 6.2 vs. 8.4 ± 2.8 µIU/mL, $p<0.001$), HOMA-IR (4.3 ± 1.5 vs. 1.8 ± 0.7, $p<0.001$), LH/FSH ratio (2.1 ± 0.8 vs. 1.0 ± 0.3, $p<0.001$), and AMH levels (7.4 ± 2.1 vs. 3.2 ± 1.1 ng/mL, $p<0.001$). PAPP-A showed significant positive correlations with HOMA-IR ($r=0.62$), IL-18 ($r=0.58$), LH/FSH ratio ($r=0.46$), and AMH ($r=0.41$) (all $p<0.01$).
Conclusion
Elevated PAPP-A levels in PCOS are associated with insulin resistance, inflammation, ovarian dysfunction, and altered gonadotropin secretion, suggesting a potential role for PAPP-A as a biomarker of disease severity.
Keywords: *PCOS, PAPP-A, Interleukin-18, HOMA-IR, AMH, LH/FSH ratio.*

Date of Submission: 08-06-2026 Date of Acceptance: 19-06-2026

I. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age and represents a major cause of anovulatory infertility worldwide. Depending on the diagnostic criteria employed, its prevalence ranges from approximately 6% to 20% among reproductive-aged women, making it a significant public health concern. [1,2] PCOS is characterized by a constellation of clinical, biochemical, and ultrasonographic features including hyperandrogenism, ovulatory dysfunction, and polycystic ovarian morphology. Beyond reproductive abnormalities, PCOS is increasingly recognized as a complex metabolic disorder associated with insulin resistance, obesity, dyslipidemia, type 2 diabetes mellitus, cardiovascular risk factors, and chronic low-grade inflammation. [3,4]

Insulin resistance is considered a central pathogenic mechanism in PCOS and is observed in a substantial proportion of affected women irrespective of body mass index. Hyperinsulinemia resulting from insulin resistance enhances ovarian androgen production, suppresses hepatic sex hormone-binding globulin synthesis, and contributes to the development of hyperandrogenism and ovulatory dysfunction.[5] Furthermore, metabolic

disturbances associated with PCOS promote a pro-inflammatory state that may contribute to long-term cardiovascular and endocrine complications.[6]

Pregnancy-associated plasma protein-A (PAPP-A) is a zinc-binding metalloproteinase belonging to the insulin-like growth factor (IGF) regulatory system. It exerts its biological action through proteolytic cleavage of insulin-like growth factor binding proteins (IGFBPs), thereby increasing local IGF bioavailability and modulating cellular growth, differentiation, and metabolic processes.[7] Emerging evidence suggests that circulating PAPP-A levels are associated with insulin sensitivity, glucose metabolism, and cardiovascular risk, indicating a potential role in metabolic disorders.[8] Altered PAPP-A concentrations have also been reported in women with PCOS, suggesting a possible link between the IGF axis, ovarian function, and metabolic abnormalities in this syndrome.[9] However, the available evidence remains limited and inconclusive.

Interleukin-18 (IL-18) is a potent pro-inflammatory cytokine belonging to the IL-1 cytokine family and plays a crucial role in both innate and adaptive immune responses. Elevated circulating IL-18 levels have been reported in women with PCOS and are believed to contribute to chronic low-grade inflammation, endothelial dysfunction, insulin resistance, and ovarian dysregulation.[10,11] Increased IL-18 concentrations have also been associated with obesity and metabolic syndrome, both of which frequently coexist with PCOS.^11 Therefore, IL-18 may serve as an important biomarker linking inflammatory and metabolic pathways in the pathogenesis of PCOS.

Given the growing evidence implicating metabolic and inflammatory mechanisms in PCOS, there is a need to further elucidate the relationship between PAPP-A and established metabolic, inflammatory, and reproductive hormonal markers. Therefore, the present study was undertaken to evaluate the association of PAPP-A with insulin resistance, IL-18, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and other metabolic and hormonal parameters in women with PCOS. Understanding these interactions may provide further insights into the pathophysiology of PCOS and identify potential biomarkers for disease severity and metabolic risk assessment.

II. Materials and Methods

Study Design and Participants

This cross-sectional analytical study was conducted in the Department of Obstetrics and Gynecology in collaboration with the Department of Biochemistry at a tertiary care teaching hospital. The study included 120 women, comprising 60 women diagnosed with polycystic ovary syndrome (PCOS) and 60 age-matched healthy controls. Women in the PCOS group were diagnosed according to the revised Rotterdam criteria, requiring the presence of at least two of the following three features after exclusion of related disorders: oligo/anovulation, clinical or biochemical hyperandrogenism, and polycystic ovarian morphology on ultrasonography. The control group consisted of healthy women with regular menstrual cycles, normal ovarian morphology, and no clinical evidence of hyperandrogenism.

Women aged between 18 and 35 years were eligible for inclusion in the study. Pregnant women and individuals with diabetes mellitus, thyroid disorders, hyperprolactinemia, Cushing syndrome, congenital adrenal hyperplasia, androgen-secreting tumors, or any other endocrine disorder known to affect ovarian function were excluded. Women receiving hormonal therapy, insulin sensitizers, corticosteroids, or medications influencing glucose metabolism or reproductive hormones within the preceding three months were also excluded.

Clinical Assessment

Detailed demographic and clinical information was obtained from all participants. Age, menstrual history, anthropometric measurements, and relevant clinical findings were recorded. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m²). Waist circumference was measured using a standardized non-stretchable measuring tape at the midpoint between the lower costal margin and the iliac crest.

Sample Collection

Following an overnight fast of 8–12 hours, approximately 5 mL of venous blood was collected from each participant under aseptic precautions. Blood samples were collected during the early follicular phase of the menstrual cycle (days 2–5) in women with regular cycles and at a corresponding time in women with irregular cycles. Samples were allowed to clot and were subsequently centrifuged at 3000 rpm for 10 minutes. The separated serum was aliquoted and stored at −80°C until biochemical and hormonal analyses were performed.

Estimation of Fasting Blood Glucose

Fasting blood glucose (FBS) levels were measured using an automated clinical chemistry analyzer employing the glucose oxidase–peroxidase (GOD-POD) enzymatic method. The results were expressed in milligrams per deciliter (mg/dL). Internal and external quality control procedures were followed throughout the study period to ensure analytical accuracy.

Estimation of Fasting Insulin

Serum fasting insulin concentrations were determined using a commercially available enzyme-linked immunosorbent assay (ELISA)/chemiluminescent immunoassay kit according to the manufacturer's instructions. The assay was calibrated using standardized controls, and results were expressed as micro-international units per milliliter (μIU/mL).

Assessment of Insulin Resistance

Insulin resistance was evaluated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), which was calculated using the following formula:

HOMA IR = Fasting insulin (μU/mL) x Fasting glucose level (mg/dl) / 405

Higher HOMA-IR values were considered indicative of increased insulin resistance.

Estimation of Pregnancy-Associated Plasma Protein-A (PAPP-A)

Serum Pregnancy-Associated Plasma Protein-A (PAPP-A) concentrations were measured using a sandwich enzyme-linked immunosorbent assay (ELISA) based on monoclonal antibody technology. The assay was performed according to the manufacturer's protocol, and absorbance was measured using a microplate reader at the specified wavelength. Concentrations were calculated from standard calibration curves and expressed in nanograms per milliliter (ng/mL).

Estimation of Interleukin-18 (IL-18)

Serum Interleukin-18 (IL-18) levels were quantified using a high-sensitivity ELISA kit employing the sandwich immunoassay principle. Standards, controls, and serum samples were analyzed in duplicate. Optical density values were measured spectrophotometrically, and concentrations were calculated using standard curves generated during each assay run. Results were expressed in picograms per milliliter (pg/mL).

Hormonal Analysis

Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and anti-Müllerian hormone (AMH) concentrations were measured using automated chemiluminescent microparticle immunoassay technology. All assays were performed according to the manufacturer's recommendations and subjected to routine quality control procedures.

LH and FSH concentrations were expressed in milli-international units per milliliter (mIU/mL). The LH/FSH ratio was subsequently calculated for each participant as an indicator of gonadotropin imbalance. Serum AMH concentrations were reported in nanograms per milliliter (ng/mL) and were used as a marker of ovarian reserve and follicular activity.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using Statistical Package for Social Sciences (SPSS) software version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Shapiro–Wilk test and expressed as mean ± standard deviation (SD). Comparisons between PCOS cases and controls were performed using the independent. Pearson's correlation coefficient was used to assess the relationship between serum PAPP-A levels and HOMA-IR, IL-18, LH/FSH ratio, AMH, and other continuous variables. A two-tailed p-value of less than 0.05 was considered statistically significant.

III. Results

Demographic Characteristics

A total of 120 women were enrolled in the study, comprising 60 women diagnosed with PCOS and 60 age-matched healthy controls. Table 1 shows the mean age of participants in the PCOS group was 25.8 ± 4.3 years compared to 24.9 ± 3.9 years in the control group, with no statistically significant difference (p=0.31). However, women with PCOS exhibited significantly higher body mass index (BMI) and waist circumference than controls. The mean BMI was 28.1 ± 3.8 kg/m² in the PCOS group compared with 23.9 ± 2.9 kg/m² in controls (p<0.001). Similarly, waist circumference was significantly increased among PCOS subjects (91.4 ± 8.2 cm vs. 78.6 ± 7.5 cm, p<0.001), indicating greater central adiposity.

Table 1. Demographic Characteristics

Parameter	PCOS (n=60)	Controls (n=60)	p-value
Age (years)	25.8 ± 4.3	24.9 ± 3.9	0.31
BMI (kg/m²)	28.1 ± 3.8	23.9 ± 2.9	<0.001
Waist Circumference (cm)	91.4 ± 8.2	78.6 ± 7.5	<0.001

Biochemical and Hormonal Parameters

Table 2 shows comparison of biochemical and hormonal parameters revealed significant metabolic and endocrine alterations in women with PCOS. Serum PAPP-A levels were significantly elevated in the PCOS group (5.8 ± 1.7

ng/mL) compared to controls (3.4 ± 1.1 ng/mL, p<0.001). Fasting blood glucose levels were higher among PCOS patients (96.8 ± 12.4 mg/dL) than controls (86.5 ± 8.6 mg/dL, p<0.001).

Table 2. Biochemical Parameters

Parameter	PCOS	Controls	p-value
PAPP-A (ng/mL)	5.8 ±1.7	3.4 ±1.1	<0.001
FBS (mg/dL)	96.8 ±12.4	86.5 ±8.6	<0.001
Insulin (µIU/mL)	18.9 ±6.2	8.4 ±2.8	<0.001
HOMA-IR	4.3 ±1.5	1.8 ±0.7	<0.001
IL-18 (pg/mL)	356 ±82	198 ±56	<0.001
LH (mIU/mL)	11.6 ±4.3	6.1 ±2.1	<0.001
FSH (mIU/mL)	5.8 ±1.4	6.2 ±1.3	0.18
LH/FSH Ratio	2.1 ±0.8	1.0 ±0.3	<0.001
AMH (ng/mL)	7.4 ±2.1	3.2 ±1.1	<0.001

Markers of insulin resistance showed marked differences between groups. Mean fasting insulin concentration was significantly increased in women with PCOS (18.9 ± 6.2 µIU/mL) compared to controls (8.4 ± 2.8 µIU/mL, p<0.001). Consequently, HOMA-IR values were significantly elevated in the PCOS group (4.3 ± 1.5) relative to controls (1.8 ± 0.7, p<0.001).

Inflammatory activity, assessed using serum IL-18 levels, was substantially higher among PCOS patients (356 ± 82 pg/mL) than healthy controls (198 ± 56 pg/mL, p<0.001). Reproductive hormone analysis demonstrated significantly elevated LH concentrations in women with PCOS (11.6 ± 4.3 mIU/mL) compared with controls (6.1 ± 2.1 mIU/mL, p<0.001), whereas FSH levels were comparable between groups (5.8 ± 1.4 vs. 6.2 ± 1.3 mIU/mL, p=0.18). As a result, the LH/FSH ratio was significantly increased in PCOS subjects (2.1 ± 0.8) compared with controls (1.0 ± 0.3, p<0.001).

Serum anti-Müllerian hormone (AMH) levels were also significantly higher in women with PCOS (7.4 ± 2.1 ng/mL) than in controls (3.2 ± 1.1 ng/mL, p<0.001), reflecting increased ovarian follicular activity characteristic of the syndrome.

Correlation Analysis

Correlation analysis performed within the PCOS group demonstrated significant positive associations between serum PAPP-A levels and several metabolic, inflammatory, and reproductive parameters. The strongest correlation was observed between PAPP-A and HOMA-IR (r=0.62, p<0.001), indicating a close relationship between elevated PAPP-A concentrations and insulin resistance. A strong positive correlation was also identified between PAPP-A and IL-18 levels (r=0.58, p<0.001), suggesting a potential link between PAPP-A and the inflammatory milieu associated with PCOS shown in Table 3 and figure 1.

Table 3. Correlation of PAPP-A with Study Variables in PCOS

Variable	r value	p value
HOMA-IR	0.62	<0.001
IL-18	0.58	<0.001
LH/FSH ratio	0.46	0.001
AMH	0.41	0.003
BMI	0.37	0.006

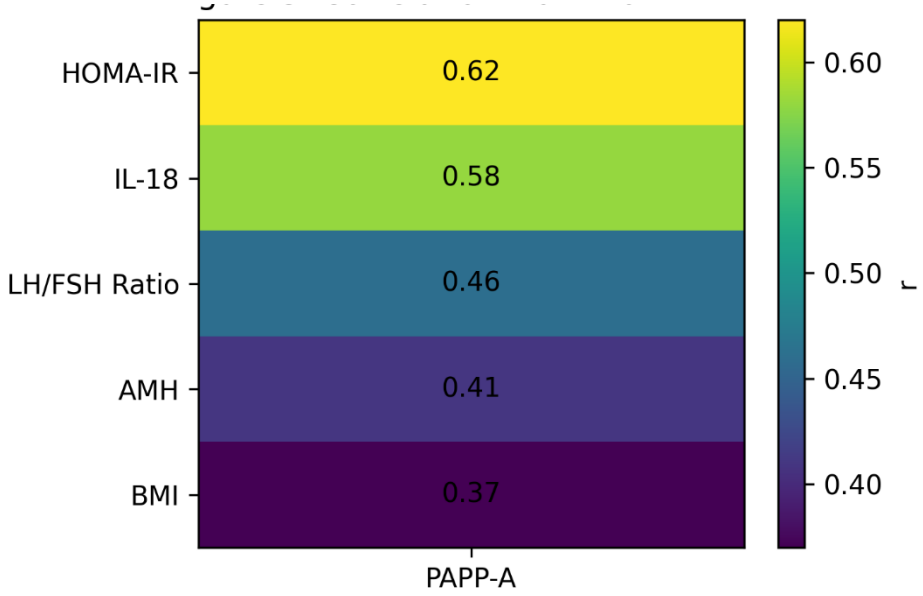

Figure 1:- Correlation matrix of PAPPA-A and study variables

Moderate positive correlations were observed between PAPP-A and LH/FSH ratio (r=0.46, p=0.001), PAPP-A and AMH (r=0.41, p=0.003), and PAPP-A and BMI (r=0.37, p=0.006). These findings indicate that increased PAPP-A levels are associated with greater metabolic dysfunction, inflammation, hormonal imbalance, and obesity in women with PCOS.

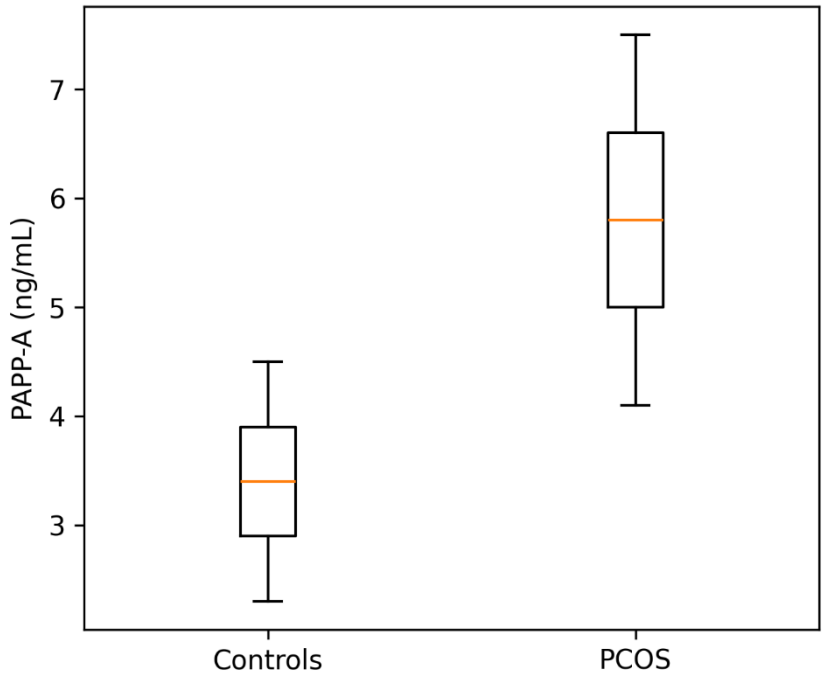

Figure 2: Comparison of PAPP-A level in cases and control group

Women with PCOS exhibited significantly elevated serum PAPP-A, insulin, HOMA-IR, IL-18, LH, LH/FSH ratio, and AMH levels compared with healthy controls shown in figure 2. Furthermore, PAPP-A demonstrated significant positive correlations with insulin resistance, inflammatory status, reproductive hormonal imbalance, and obesity, supporting its potential role as a biomarker of metabolic and endocrine dysfunction in PCOS.

Table 3. Correlation of PAPP-A with Study Variables in PCOS

Variable	r value	p value
HOMA-IR	0.62	<0.001
IL-18	0.58	<0.001
LH/FSH ratio	0.46	0.001
AMH	0.41	0.003
BMI	0.37	0.006

IV. Discussion

Polycystic ovary syndrome (PCOS) is a complex endocrine-metabolic disorder characterized by reproductive dysfunction, insulin resistance, chronic low-grade inflammation, and altered folliculogenesis. In the present study, women with PCOS demonstrated significantly elevated serum PAPP-A, IL-18, fasting insulin, HOMA-IR, LH/FSH ratio, and AMH levels compared with healthy controls. Furthermore, serum PAPP-A showed significant positive correlations with HOMA-IR, IL-18, LH/FSH ratio, and AMH, suggesting a possible association between PAPP-A and both metabolic and reproductive abnormalities in PCOS.

The mean age of women in the PCOS and control groups was comparable, minimizing age-related confounding. However, BMI and waist circumference were significantly higher in women with PCOS. These findings are consistent with the established association between PCOS and obesity, particularly central adiposity, which contributes to insulin resistance and chronic inflammation through adipokine dysregulation and altered cytokine secretion.[12]

One of the principal findings of the present study was the significantly elevated serum PAPP-A concentration among women with PCOS. PAPP-A is a metalloproteinase involved in cleavage of insulin-like growth factor binding proteins (IGFBP-4 and IGFBP-5), thereby increasing local insulin-like growth factor (IGF) bioavailability. Increased IGF signaling has been implicated in ovarian steroidogenesis, follicular recruitment, and androgen production.[13]

Our findings are partially supported by the study of Öztürk et al., who evaluated serum PAPP-A concentrations in 62 women with PCOS and reported significantly higher PAPP-A levels in lean PCOS women compared with BMI-matched controls, suggesting that PAPP-A may reflect intrinsic metabolic and endocrine disturbances independent of obesity.[14] Although overall PAPP-A concentrations were not significantly different between all PCOS patients and controls in their study, subgroup analyses demonstrated a significant increase among lean PCOS patients, indicating a potential role of PAPP-A in disease pathogenesis.[14] The stronger association observed in our study may be attributable to the inclusion of patients with more pronounced metabolic abnormalities.

The biological plausibility of elevated PAPP-A in PCOS is further supported by studies demonstrating the presence of PAPP-A within ovarian follicles and its association with intrafollicular hormone levels. PAPP-A has been shown to regulate follicular growth through modulation of IGF activity and granulosa cell function, suggesting that dysregulated PAPP-A expression may contribute to the arrested follicular development characteristic of PCOS.[15]

Insulin resistance remains one of the hallmark metabolic abnormalities in PCOS. In the present study, fasting insulin and HOMA-IR were significantly elevated among women with PCOS. Moreover, serum PAPP-A demonstrated a strong positive correlation with HOMA-IR. These findings support the concept that PAPP-A may be linked to metabolic dysfunction and insulin signaling pathways. Hyperinsulinemia enhances ovarian androgen synthesis, suppresses hepatic sex hormone-binding globulin production, and contributes to anovulation and follicular arrest.[16]

The inflammatory milieu associated with PCOS was reflected by significantly elevated IL-18 levels in the present study. IL-18 is a pro-inflammatory cytokine belonging to the IL-1 family and has been implicated in obesity, insulin resistance, endothelial dysfunction, and atherosclerosis. Elevated IL-18 concentrations have been reported in several studies involving women with PCOS.[17]

Yang et al. reported significantly increased serum IL-18 levels in women with PCOS, particularly among those with insulin resistance. The investigators demonstrated positive correlations between IL-18 and BMI, HOMA-IR, testosterone levels, and LH/FSH ratio, suggesting that IL-18 may represent an important link between metabolic and reproductive abnormalities in PCOS.[18] Similar observations were reported by Escobar-Morreale and colleagues, who proposed that chronic low-grade inflammation contributes substantially to insulin resistance and hyperandrogenism in PCOS.[19]

Our observation of a positive correlation between PAPP-A and IL-18 suggests that PAPP-A may also participate in inflammatory pathways. Although direct mechanistic evidence remains limited, PAPP-A expression has been shown to increase within inflamed vascular tissues and atherosclerotic plaques, supporting its role as a marker of inflammatory activity. Consequently, elevated PAPP-A concentrations in PCOS may reflect both metabolic dysfunction and chronic systemic inflammation.[20]

The present study also demonstrated significantly elevated LH levels and LH/FSH ratios in women with PCOS. Increased pulsatile gonadotropin-releasing hormone (GnRH) secretion preferentially stimulates LH secretion, resulting in ovarian theca-cell hyperactivity and excess androgen production.[21] The positive correlation between PAPP-A and LH/FSH ratio observed in our study suggests that PAPP-A may be associated with neuroendocrine abnormalities characteristic of PCOS.

AMH levels were significantly elevated among women with PCOS and demonstrated a moderate positive correlation with PAPP-A. Elevated AMH is a well-established feature of PCOS and reflects increased numbers of small antral follicles together with impaired follicular maturation.[22] Experimental evidence suggests that PAPP-A regulates follicular IGF bioavailability and granulosa cell function. Therefore, the positive association between PAPP-A and AMH may indicate a role for PAPP-A in abnormal folliculogenesis and ovarian reserve dynamics.[15]

Collectively, our findings support the concept that PAPP-A occupies a unique position at the intersection of metabolic, inflammatory, and reproductive pathways. Elevated PAPP-A levels may reflect enhanced IGF signaling, insulin resistance, inflammatory activation, and altered ovarian follicular development. Such multifaceted involvement suggests that PAPP-A could potentially serve as an integrated biomarker for assessing disease severity in women with PCOS.

Strengths of the Study

The present study simultaneously evaluated metabolic, inflammatory, and reproductive hormonal parameters in women with PCOS. Additionally, correlation analyses involving PAPP-A, HOMA-IR, IL-18, AMH, and LH/FSH ratio provided insight into possible pathophysiological interactions among these variables.

V. Limitations

The study was cross-sectional in design and therefore cannot establish causal relationships. The sample size was relatively modest, and the findings require validation in larger multicentric cohorts. Furthermore, dynamic insulin sensitivity assessments such as euglycemic-hyperinsulinemic clamp studies were not performed. Future prospective studies incorporating molecular markers of IGF signaling may provide additional mechanistic insights.

VI. Conclusion

Women with PCOS demonstrated significantly elevated serum PAPP-A, IL-18, fasting insulin, HOMA-IR, LH/FSH ratio, and AMH levels compared with healthy controls. Serum PAPP-A showed significant positive correlations with insulin resistance, inflammatory status, ovarian reserve markers, and gonadotropin imbalance. These findings suggest that PAPP-A may serve as a promising biomarker reflecting the complex interplay between metabolic, inflammatory, and reproductive dysfunction in PCOS.

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