Journal of Rare Cardiovascular Diseases
ISSN: 2299-3711 (Print) | e-ISSN: 2300-5505 (Online)
www.jrcd.eu
RESEARCH ARTICLE

Exploring Hidden Biological Landscapes and Physiological Interplay in Polycystic Ovary Syndrome: Insights into Kininogen-1, PDGF, and AMH Hormone in Samarra

Mohammed Khattab Omar Al-Samarrai[1], Rasha Kanaan Mohammed[2] Maysaa Tarik Hanoon[3] and Suzan Najim Abdullah[4]

[1]Msc Nursing student, Bharati Vidyapeeth (Deemed to be University), College of Nursing Sangli.
[2]Professor, Bharati Vidyapeeth (Deemed to be University), College of Nursing Sangli.
[3]Assistant Professor, Bharati Vidyapeeth (Deemed to be University), College of Nursing Sangli.
[4]Clinical Instructor, Bharati Vidyapeeth (Deemed to be University), College of Nursing Sangli.

*Corresponding Author
Mohammed Khattab Omar Al-Samarrai
(m.khattab@uosamarra.edu.iq)

Article History
Received: 28.06.2025
Revised: 06.07.2025
Accepted: 14.08.2025
Published: 02.09.2025

Abstract: The study included 67 married women who attended private medical laboratories in Samarra and its surrounding areas, comprising 50 patients diagnosed with polycystic ovary syndrome (PCOS) and 17 healthy controls, during the period from October 2024 to January 2025. The participants' ages ranged from 26 to 37 years, for each participant, 5 ml of venous blood was collected using a sterile syringe and transferred into a clot-activator-free test tube. The samples were allowed to stand for 15 minutes and then centrifuged at 3000 rpm to separate the serum from the cellular components. The serum was subsequently stored at −20°C until laboratory analyses were performed. Serum levels of Kininogen-1 (KNG1), Platelet-Derived Growth Factor (PDGF), and Anti-Müllerian Hormone (AMH) were measured using the enzyme-linked immunosorbent assay (ELISA) technique. The results demonstrated a statistically significant decrease in serum KNG1 and PDGF levels in the patient group compared to the control group ($P \leq 0.05$). In contrast, AMH levels were significantly elevated in women with PCOS relative to healthy controls ($P \leq 0.05$). This finding supports the conclusion that elevated AMH is a hallmark feature of PCOS, reflecting the increased number of small antral follicles and impaired ovarian function in affected women and suggest that Kininogen-1 may contribute to the development of insulin resistance in women with PCOS, thereby exacerbating metabolic deterioration. PDGF appears to play a critical role in chronic ovarian inflammation associated with PCOS, enhancing interactions between ovarian cells and their surrounding environment, which may promote ovarian thickening and the formation of damaged tissue

Keywords Kininogen-1, PDGF, AMH, PCOS.

INTRODUCTION

Polycystic ovary syndrome (PCOS) was first described in 1935 by Stein and Leventhal, who reported the condition in women presenting with amenorrhea, hirsutism, and ovarian enlargement [1]. PCOS is considered one of the most common endocrine disorders among women of reproductive age, affecting approximately 15–20% of this population [2]. The syndrome is classified as a heterogeneous condition, with manifestations varying among affected women, including menstrual irregularities, weight gain, acne, hirsutism, and infertility [3].

Studies have shown that nearly 26% of women with PCOS experience insulin resistance (IR), leading to hyperinsulinemia, which is closely associated with an increased risk of metabolic disturbances such as type 2 diabetes mellitus, hypertension, and obesity [4]. These conditions are often accompanied by clinical features such as hirsutism, metabolic disorders, elevated blood pressure, and obesity [5].

Furthermore, it has been reported that up to 70% of women with PCOS suffer from insulin resistance, in addition to the presence of chronic low-grade inflammation, reflected by elevated levels of inflammatory markers such as KBG-1, PDGF, and TNF-α [6]. Consequently, these women are at higher risk of developing hypertension, severe obesity, and future cardiovascular diseases [5].

Polycystic ovary syndrome (PCOS) is a hereditary and heterogeneous condition. One of its hallmark features is hyperandrogenism, which manifests variably among affected women. This disorder is characterized by elevated levels of androgens such as testosterone, leading to clinical manifestations including:

1. Hirsutism: Excessive hair growth in areas uncommon for women.
2. Menstrual irregularities: Such as oligomenorrhea or amenorrhea.
3. Acne: Increased prevalence of acne due to elevated androgen levels.

Studies indicate that these symptoms can vary considerably between individuals, making PCOS a heterogeneous condition that requires precise diagnosis and individualized treatment based on the predominant symptoms in each case [7].

Several factors contribute to the development and progression of PCOS. Insulin resistance is a major

contributor, predisposing many women with the syndrome to type 2 diabetes mellitus [8]. Obesity is also closely associated with PCOS, significantly influencing both the severity of symptoms and the overall health of patients. Additionally, women with PCOS may face an increased risk of recurrent miscarriage, reflecting the syndrome's impact on reproductive outcomes [9]. The condition is further linked to cardiovascular diseases (CVD), highlighting the broader systemic risks for affected individuals [10]. Finally, chronic inflammation plays a key role in exacerbating the symptoms and contributing to the progression of the syndrome [11].

Kainongen-1 is a protein or cellular factor involved in various biological processes within cells, exerting multiple effects on cell growth regulation, metabolism, and tissue function. In recent years, this protein has attracted significant attention in medical and scientific research due to its association with numerous diseases and hormonal disorders, including polycystic ovary syndrome (PCOS) and certain cancers.

Recent studies suggest that Kainongen-1 may influence the responsiveness of ovarian reproductive cells to hormones. In women with PCOS, abnormal levels of hormones such as androgens and follicle-stimulating hormone (FSH) are commonly observed, leading to impaired ovulation and follicular maturation. Research indicates that Kainongen-1 may play a role in regulating these hormonal responses within the ovaries, ultimately affecting menstrual cycles and fertility [12].

Elevated levels of Kainongen-1 in the ovaries or surrounding tissues may stimulate the growth of immature follicles, exacerbating ovulatory dysfunction in PCOS. This is often associated with androgen accumulation in the body, resulting in clinical manifestations such as hirsutism or acne. While some evidence suggests that Kainongen-1 may be part of the mechanism regulating cellular responses to androgens, research on this role remains in its early stages [13].

In some cases, Kainongen-1 has been linked to abnormal insulin levels, contributing to insulin resistance in individuals with PCOS. Insulin resistance can have serious health consequences, including type 2 diabetes and cardiovascular disease. Studies suggest that modulating Kainongen-1 levels may help restore hormonal balance in pathological conditions associated with insulin dysregulation [14].

Platelet-derived growth factor (PDGF) is a protein considered one of the key regulators of cell growth and proliferation, playing a vital role in tissue repair and regeneration [15]. PDGF primarily stimulates the growth of stem cells, muscle cells, and connective tissue cells, and it also contributes to wound healing and vascular regulation [16].

One of the primary functions of PDGF is to stimulate cell proliferation in damaged tissue areas. Upon tissue injury, PDGF is secreted by platelets at the injury site, activating local cells to repair damage and regenerate the affected tissue [15]. PDGF is a crucial factor in promoting the proliferation of muscle cells and fibroblasts, thereby enhancing the wound healing process [15]. PDGF also plays a role in stimulating the formation of new blood vessels, a process known as angiogenesis. This facilitates increased blood flow to damaged tissues by promoting vascular growth, which is essential for wound repair and the restoration of normal tissue function following injury [16,15].

Due to its critical role in cell growth and vascular formation, dysregulation of PDGF levels has been linked to several diseases. For instance, in certain cancers, PDGF overexpression can promote tumor growth and metastasis , Excessive PDGF may also contribute to the formation of vascular tumors [17].

Anti-Müllerian Hormone (AMH) is a glycoprotein produced primarily by granulosa cells in the small and pre-antral ovarian follicles and serves as a key marker for ovarian reserve, reflecting the number of remaining follicles in the ovary [18]. AMH levels remain relatively stable throughout the menstrual cycle, making it a reliable indicator of ovarian function at any stage [19]. In women with polycystic ovary syndrome (PCOS), AMH levels are often significantly elevated compared to healthy women, mainly due to an increased number of small, immature follicles that secrete AMH in higher quantities [20].

These immature follicles contribute to impaired ovulation, explaining the menstrual irregularities and infertility commonly associated with PCOS [21]. Recent studies indicate that elevated AMH is directly linked to the number of small, underdeveloped follicles in the ovary, which leads to suppression of granulosa cell responsiveness to FSH, thereby inhibiting proper follicular growth and maturation [22]. This suppression is considered a major factor in ovulatory dysfunction and delayed conception in women with PCOS.

Furthermore, elevated AMH has been associated with obesity, as studies have shown that women with PCOS and higher body mass index (BMI) often present with higher AMH levels, exacerbating ovulatory disturbances [23]. Additionally, women with higher AMH concentrations frequently exhibit more pronounced clinical features of PCOS, including hirsutism and metabolic abnormalities [24]. Although AMH is a valuable indicator of follicle count, its use as a standalone diagnostic tool for PCOS remains limited; it should be interpreted within a comprehensive clinical context, including hormonal profiling and assessment of clinical symptoms [2]. Therefore, AMH serves as a crucial marker for assessing ovarian reserve, understanding ovarian dysfunction in PCOS, guiding therapeutic strategies, and improving ovulatory outcomes [18,21]

MATERIALS AND METHODS:

The present investigation was carried out in private medical clinics located in Samarra, within Salah al-Din governorate, Iraq. The work extended over the period from October 2024 to January 2025. Participants were men aged between 26 and 37 years, with a total sample size of 70 subjects. Of these, 17 served as the control group, while 50 were assigned to the patient group. All individuals voluntarily agreed to take part in the study and underwent hormonal and biochemical analyses, including Kininogen-1, PDGF and AMH

Inclusion criteria

Patients clinically presented with PCOs were included in this study, which the specialist doctors and variables investigations were diagnosed these diseases.

Samples collection

A 5 ml blood sample was taken in a plain tube and allowed to stand for about 20 to 30 minutes for clot formation. It was then centrifuged using a macrocentrifuge for 5 to 15 minutes at a speed of 3000 rpm. The resulting fresh, non-hemolyzed serum was collected and stored in a deep freeze at -20°C.

Ethical Approval and Informed Consent

All procedures involving human participants were performed in accordance with the ethical guidelines of the institutional research committee and the 1964 Helsinki Declaration. No participants were harmed. Blood samples were collected only after obtaining informed consent, and all participants were fully aware of the study purpose and their right to participate voluntarily or withdraw at any time

Levels of variables (Kininogen-1, PDGF, and AMH) were estimated by using the Enzyme Linked ImmunoSorbant Assay (ELISA) kit from (Elkbiotechnology -USA, and Sunlong.China); This test measures the amount of the variables in blood serum using also the Enzyme Linked Immuno Sorbant Assay (ELISA) .

Bio-Statistical Analysis

The results were triplicated, expressed as mean ± SD due to results may be higher or lower than standard deviation. *T*-test was used by SPSS software on computer version 23 for assessment of the results. Significant variation was considered when the P value less than 0.05.

RESULTS AND DISCUSSION

Kininogen-1 levels in Study groups

The results indicated that the mean ± standard deviation of Kininogen-1 levels in the patient group was 1.972 ± 0.66 ng/ml, whereas the control group showed a mean of 3.885 ± 0.35 ng/ml, as presented in Figure 1. A statistically significant decrease was observed in the patient group compared to the controls at a significance level of $P \leq 0.05$

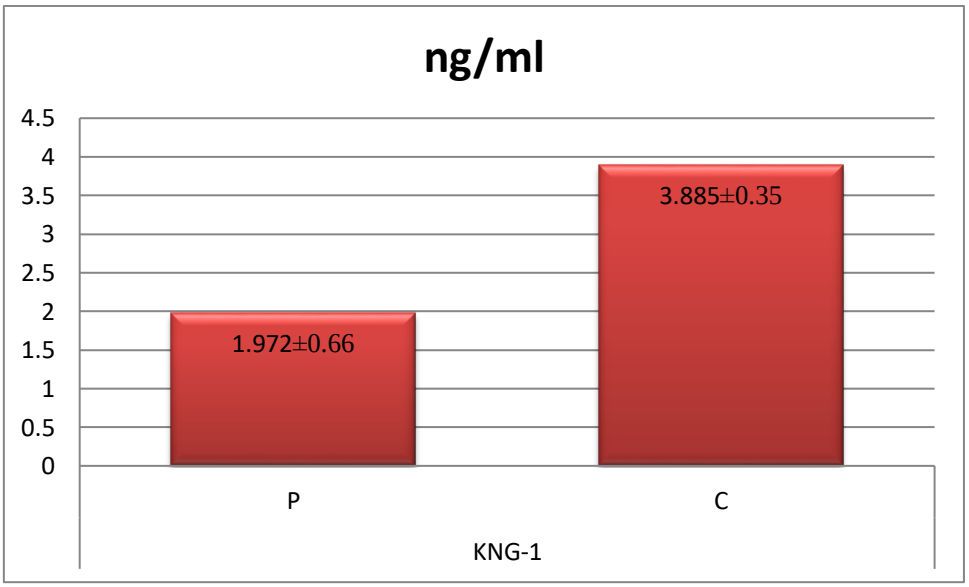

Figure 1 Kininogen-1 (KNG1) levels in the study groups.

The findings of this study align with those reported by Khan et al. [25], who observed reduced Kininogen-1 (KNG1) levels in women with polycystic ovary syndrome (PCOS). KNG1 is a key regulator of inflammatory processes, capable of increasing vascular permeability and promoting the release of inflammatory mediators. Chronic inflammation has been suggested as a contributing factor in the onset and progression of PCOS [26,27]. Moreover, Khan et al. [25] reported a strong association between KNG1 and the development of reproductive disorders.

In women with PCOS, serum KNG1 levels are decreased, while progesterone has been shown to enhance KNG1 expression in granulosa cells of the ovary. Changes in serum protein profiles appear to be linked to progesterone levels, which improve ovarian function by upregulating the expression of EREG, Inhibin βA, IDE, PDGF-D, and KNG1.

PCOS is recognized as a major cause of infertility [28,29]. Hormonal imbalances in affected women, such as elevated estrogen, increased androgens, reduced progesterone, or combinations of these abnormalities, complicate therapeutic interventions [30]. While standard treatment strategies often rely on estrogen antagonists like clomiphene citrate to stimulate ovulation, or anti-androgens such as flutamide to reduce hyperandrogenism, supplementing progesterone alongside conventional therapies may enhance treatment efficacy. This approach could also help prevent miscarriage and preterm birth, particularly in women with low progesterone levels.

KNG1 serves as the primary source for bradykinin (BK), a potent peptide that induces vasodilation, increases vascular permeability, and mediates pain sensation. As such, high-molecular-weight KNG1 (HK) is a central component of the body's inflammatory response. BK also plays a role in blood pressure regulation by promoting vasodilation and consequently reducing blood pressure [31].

Therefore, the observed decrease in KNG1 levels in women with PCOS has significant implications, particularly for ovarian function and metabolic health. KNG1 is a precursor to kinins, which are involved in numerous physiological processes including inflammation and blood pressure regulation. In the context of PCOS, reduced KNG1 may be linked to hormonal and metabolic imbalances characteristic of the syndrome. This reduction is associated with lower progesterone levels, a common feature in PCOS, potentially impairing granulosa cell function and thereby adversely affecting ovarian health and fertility [32].

Platelet-Derived Growth Factor (PDGF) levels in Study groups:
The results showed that the mean ± standard deviation of platelet-derived growth factor (PDGF) levels in the patient group was 145.17 ± 31.42 pg/ml, whereas in the control group it was 331.44 ± 51.14 pg/ml, as illustrated in Figure 2 significant decrease was observed in the patient group compared to the control group at a probability level of $P \leq 0.05$

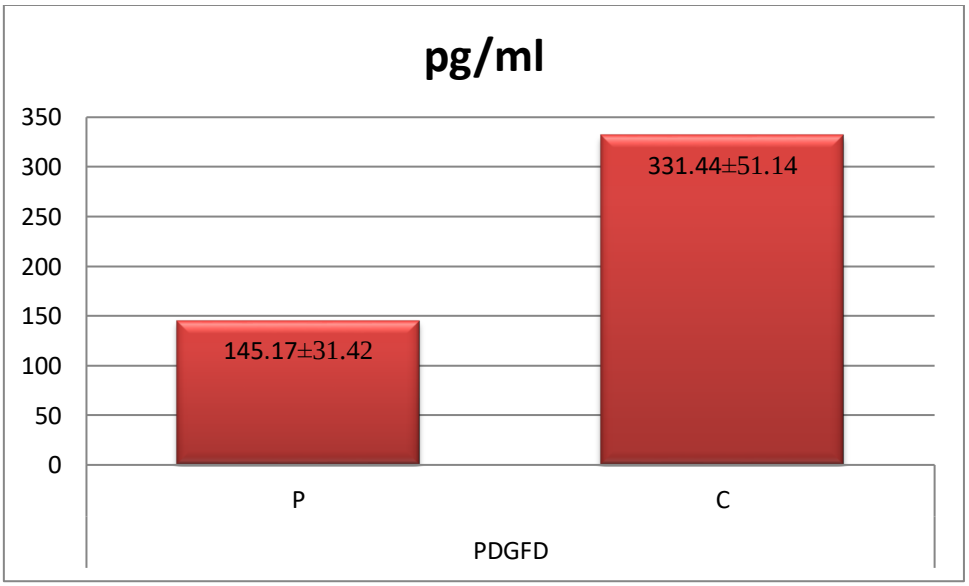

Figure 2 The platelet-derived growth factor (PDGF) levels in the study groups.

The findings of this study are consistent with those reported by Shivhare et al. [33] and Di Pietro et al. [34], who observed reduced levels of platelet-derived growth factor (PDGF) in women with polycystic ovary syndrome (PCOS).

Cellular growth regulation within the ovary relies heavily on a network of biochemical signals, including growth factors such as PDGF and EGF. PDGF-D, in particular, is a critical mediator that promotes ovarian cell proliferation and contributes to the regulation of follicular growth and maturation. According to Chang et al. [35], PDGF-D plays a central role in maintaining a balance between proliferative and regulatory processes within ovarian cells, acting as a key modulator that can either enhance or restrict cellular proliferation depending on local physiological conditions [36].

In PCOS, disruptions in PDGF-D secretion are part of the underlying mechanisms leading to hormonal imbalances, including elevated androgen levels and reduced progesterone production. Low PDGF-D levels may hinder the maturation

of ovarian follicles, resulting in ovulatory dysfunction and recurrent anovulation, which are major contributors to infertility commonly associated with PCOS [37].

Multiple studies have demonstrated a clear link between decreased PDGF-D and the development of ovarian cysts. Insufficient PDGF-D contributes to cellular disturbances within the ovary, delaying follicle formation or halting their development entirely, thus preventing normal maturation [38]. For instance, Zheng et al. [39] reported that reduced PDGF-D in PCOS patients correlates directly with lower ovulatory efficiency and impaired reproductive outcomes.

Other growth factors, such as EGF and KNG1, support ovarian hormonal functions by facilitating intercellular interactions and promoting balanced hormonal activity within follicles. Consequently, PDGF-D deficiency in PCOS may disrupt this complex hormonal and biochemical network [40].

Recent evidence also suggests that restoring PDGF-D levels could serve as a therapeutic strategy to improve ovarian function in women with PCOS. Such interventions may alleviate infertility-related symptoms, particularly when combined with treatments targeting progesterone or androgen regulation to achieve better hormonal balance [41].

Overall, the growing body of evidence indicates that PDGF-D deficiency in PCOS not only contributes to reduced fertility but also plays a central role in the development of ovarian and hormonal disturbances associated with the syndrome, highlighting the importance of early diagnosis and effective management , the results of this study contrast with those reported by Gao et al. [42], who found a significant increase in PDGF levels in the serum of women with PCOS

Anti-Müllerian Hormone (AMH) Levels in Study Groups

The results indicated that the mean ± standard deviation of anti-Müllerian hormone (AMH) levels in the patient group was 6.13 ± 1.9 ng/ml, whereas the control group exhibited a mean of 2.44 ± 0.42 ng/ml, as shown in Figure 3. A statistically significant increase was observed in the patient group compared to the controls at a significance level of $P \leq 0.05$

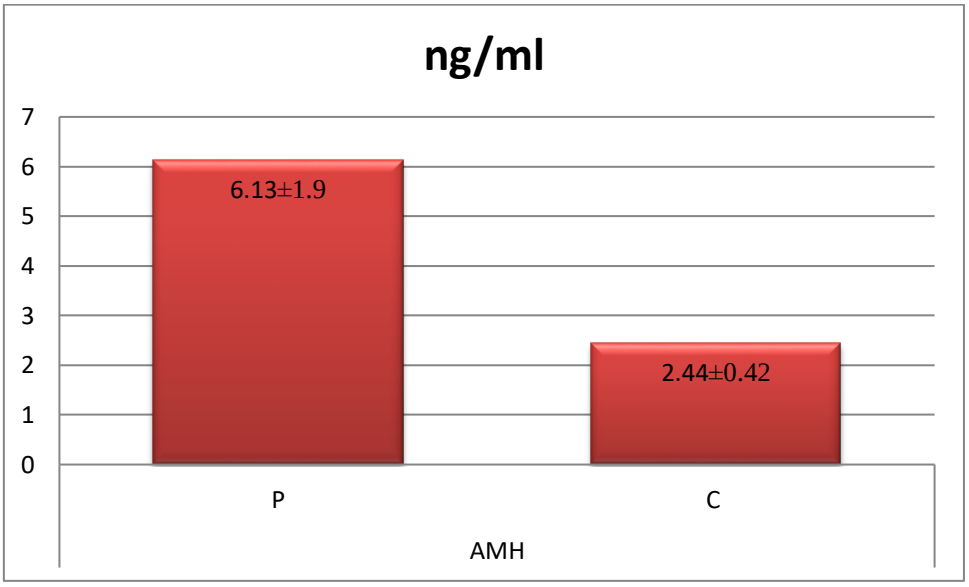

Figure 3 Müllerian hormone (AMH) levels in the study groups.

Polycystic ovary syndrome (PCOS) is often associated with a greater number of small antral follicles in the ovaries compared to women without the condition. Because anti-Müllerian hormone (AMH) is mainly secreted by the granulosa cells of these small follicles, an increase in follicle number naturally leads to higher circulating AMH levels [43,45].

Moreover, granulosa cells in PCOS appear to produce AMH at a higher rate on a per-cell basis. This means that even when accounting for the increased number of follicles, the hormone levels in PCOS patients are amplified due to enhanced secretion by individual cells [44].AMH also plays an active role in disrupting normal follicular development. Elevated AMH reduces follicle sensitivity to follicle-stimulating hormone (FSH), preventing the maturation of small antral follicles. This establishes a cycle in which persistent small follicles maintain high AMH levels, which in turn further inhibits follicular growth and ovulation [44,45].

Hormonal factors, including increased androgens, elevated luteinizing hormone (LH), and insulin resistance, interact with ovarian follicles to further influence AMH production. Androgens can stimulate the proliferation of small follicles and may enhance AMH

expression. In addition, AMH may act on hypothalamic neurons that regulate GnRH, contributing to altered LH secretion and further interference with normal follicular development [45,46].

Genetic variations also contribute to differences in AMH levels between individuals. Polymorphisms in AMH or its receptor gene (AMHR2), as well as differences in promoter activity, may increase AMH production in certain patients, partially explaining the variability in serum levels [47].

From a clinical perspective, elevated AMH serves as a useful marker for polycystic ovarian morphology and may support the diagnosis of PCOS, although it should not replace established clinical and ultrasonographic criteria. High AMH levels can also predict a strong ovarian response to stimulation, helping clinicians adjust treatment strategies and reduce the risk of overstimulation. Addressing hormonal imbalances, such as reducing androgen excess or improving insulin sensitivity, may help normalize follicular development and modulate AMH production [45,48].

Acknowledgments

We extend my heartfelt appreciation to the medical laboratories for their invaluable cooperation and assistance throughout this study. Their expertise and support in conducting the necessary tests and providing accurate data were essential to the completion of this research. We are also profoundly thankful to all the participants who generously offered their time and effort, making this study possible. Their trust, patience, and willingness to contribute significantly enriched the quality and outcomes of this work.

Conflicts of Interest

The authors declares that there are no conflicts of interest related to this study

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