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RESEARCH ARTICLE

Hormonal imbalance and Systemic Inflammation in Women with PCOS: A Case Control Study from Iraq

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Abstract: *Background:* Polycystic ovary syndrome (PCOS) is an endocrine disorder that is very common and can affect 5-15% of women of reproductive age in the world. This study addresses the associations of hormonal dys-regulation with inflammatory markers as possible early risk regulators of CVD in PCOS. Methods: A case–control study enrolled 90 women (30 healthy controls and 60 with PCOS stratified by age: 20–30 and 30–40 years). Participants were stratified by residence (urban/rural). Serum hormonal profiles (LH, FSH, estradiol, progesterone, testosterone) and inflammatory markers (IL-6, TNF-α, hs-CRP) were measured by ELISA. Pearson correlation and multiple linear regression (adjusted for age, BMI) assessed associations. *Results:* Women with PCOS demonstrated elevated LH (12.8±3.4 and 14.2±3.8 IU/L; p<0.001), testosterone (72.4±18.9 and 79.6±21.1 ng/dL; p<0.001), with reduced estradiol (95.5±30.2 and 82.1±27.9 pg/mL; p<0.001) and progesterone (3.1±1.0 and 2.6±0.9 ng/mL; p<0.001). Inflammatory markers were significantly elevated: IL-6 (4.8±1.5 and 5.6±1.7 pg/mL, p<0.001), TNF-α (12.3±4.2 and 13.8±4.6 pg/mL, p<0.001), hs-CRP (4.1±1.7 and 4.8±1.9 mg/L, p<0.001). Urban residence was associated with higher inflammatory markers (IL-6: 5.2±1.4 versus 4.3±1.2 pg/mL, p=0.04). *Conclusions:* Despite hormones being considered as the primary cause of PCOS features, elevated systemic inflammatory markers have also been associated with PCOS, especially in urban and older populations. The combination assessment of hormone and immunological parameters can be used to determine the early diagnosis of CVD risk. Autonomic indices derived from the heart (e.g. heart rate variability) were also not measured and should be a priority for future studies.

Keywords: Cardiovascular risk; case control study; cytokines; hormonal imbalance; polycystic ovary syndrome; systemic inflammation

INTRODUCTION

Polycystic ovary syndrome is a common endocrine disease of women of reproductive age and occurs between 5-15% of the female population around the world, depending on the diagnostic criteria and population studied [2-3]. While traditionally being defined by reproductive dysfunction (oligo/anovulation, hyperandrogenism and polycystic ovarian morphology), the modern conception of PCOS is one that is a systemic metabolic disorder with important extragonadal consequences [3,4].

Metabolic consequences of PCOS are much farther than the reproductive pathology. Insulin resistance has been reported to be present in approximately 50-70% of patients with PCOS, which is significantly higher than there is in body mass index matched controls [3]. This metabolic disorder is found to be associated with atherogenic dyslipidemia, which is defined by the elevation of triglycerides and the lowering of high-density lipoprotein cholesterol (HDL-C) [2]. Furthermore, women with PCOS have two to three fold increased risk of cardiovascular disease and metabolic syndrome compared to age matched controls [6].

Recent evidence has indicated chronic low-grade inflammation to be an important mediator in cardiovascular pathology in PCOS. Multiple studies have reported elevated pro-inflammatory cytokines including interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-alpha) and high sensitivity C-reactive protein (hs-CRP) in PCOS populations [8,6]. These inflammatory markers are correlated with the degree of insulin resistance, the degree of endothelial dysfunction and the rate of progression of atherosclerosis [8]. Monocyte-derived macrophages that are activated and generation of more reactive oxygen species are inflammatory mechanisms that are more likely to cause vascular wall damage in PCOS [6].

Pathophysiology is still not completely understood but there is increasing evidence that autonomic nervous system (ANS) dysplasia may be a major contributor to the prominent cardiovascular-related risk in PCOS [7]. Though HRV (a validated noninvasive measure of the cardiac autonomic nervous system's function) is reported to be decreased in some PCOS cohorts, advanced studies linking hormonal parameters, systemic inflammation and autonomic function are still scarce, particularly in the Middle Eastern population. [8].

The presence of physiological changes that predispose to cardiovascular complications early in the course might enable implementation of specific preventive interventions [9]. The current study was therefore undertaken to evaluate relationships between hormonal dysregulation and such inflammatory markers of an Iraqi population stratified by age and urban/rural facto

to study potential environmental modifiers of the disease phenotypes.

MATERIAL AND METHODS

Study Design and Setting

In this case control study, the study was done at Salah Al-Din teaching hospital, Tikrit teaching hospital and some other clinics in Tikrit (Iraq) between January 20, 2024 June 20, 2025. The study protocol had been approved by the ethical committee of the institute (Reference Number: 11557-T, Approval Date: January 15, 2024). All procedures were in accordance with the Declaration of Helsinki statements and all patients gave a written informed consent before enrolment. Special consideration was given to the confidentiality of the participants, therefore individual personal data was not gathered from the study records but codes were used to identify the patients. This study is performed by using the STROBE statement for observational studies.

Study Participants

A total of 90 women were recruited with three groups of 30 women from the following groups:
Group 1 (Control): Normal women (aged between 20-40 years) cycle (21-35 days); no clinical or laboratory data of endocrine disorder; with ovulatory function being verified; transvaginal ultrasound examination of the ovaries: With normal morphology (presence of the mid-luteal trophe of progesterone [>=3 ng/mL]).

PCOS aged 20-30 years (group 2): women 20-30 years old with PCOS diagnosed according to Rotterdam criteria [(met (?2 of: oligo/anovulation, biochemical or clinical hyperandrogenism or polycystic ovarian morphology) [5].

Group 3 (PCOS 30-40 years): Women aged 30-40 years that fit the same diagnosis of PCOS as Group 2.

For the assessment of environmental influences on inflammatory variables subjects within PCOS cohorts were sampled within the PCOS cohorts to reside in an urban (n=10) or rural (n=10) environment and characterized by maternal socioeconomic status.

Sample Size Estimation

Sample size calculation a priori (based on the expected difference in inflammatory markers between the PCOS vs. control groups which should be moderate to high (f=0.30), a=0.05 and power 0.80) showed that minimum number of study subjects should be 84. Need for better control We had adequate power (greater than .75) for first row (with primary differences across group).

Inclusion and Exclusion criteria

Inclusion criterion: Women (20-40 years) with diagnosis of PCOS or with normal endocrine profile with wide written - informed consent.
Exclusion criteria: pregnant women/ women in lactation period; chronic systemic diseases: DM, hypertension, thyroid dysfunction, hormonal drugs within the past 3 months; acute infection 4 weeks, smoking, frequent use anti-inflammatory drugs;

Clinical Assessment and Sample Collection

Medical history and blood pressure, anthropometric variables (Height, weight and waist circumference) were noted. When hormones are under study, serum collected at an early follicular phase (cycle day 3-5) at 08.00 -10:00 AM after an Overnight fast (to rule out the influences of circadian and menstrual phases). Ovulatory period interrelated with sampling time in the period of early follicular (last period date, or positive serum progesterone level <1 ng/ml) in women with anovulatory PCOS. Serum was centrifuged at 3000g per 10 min and stored at -20 deg C. The entire laboratory examinations have been conducted in 6 months of sample collection.

Laboratory Methods

Hegonadotrophin (luteinizing hormone [LH] and follicle stimulating hormone [FSH]) levels of serum GH, serum gonadotrophin levels, oestrogens (17a-estradiol), progesterone and testosterone were done using commercial enzyme immunoassays (Immuno-Biological Laboratories, Inc., Minneapolis, MN, USA). Inflammatory variables - interleukin (IL)-6 (IL-6; Cat # IBL-27015, sensitivity 0.2 pg/mL intra-assay CV 6.5%), tumor necrosis factor alpha (TNF-alpha; Cat # IBL-27016, sensitivity 0.2 pg/mL intra-assay CV 8.1%)

Statistical Analysis

The analysis of data was done through statistical package of the social sciences (SPSS). (IBM Corporation, Armonk NY) (version 26.0). Descriptive statistics were provided in terms of mean and standard deviation. Shapiro-Wilk test, distribution normality test. The one-way/ANV and the pairwise comparisons Post Income Bonferonni adjusted were used to compare continuous normally distributed variables. Since the normality distribution of the variables (inflammatory markers) was not realized, the inflammatory markers showed were taken in logs and results of inverse log transformation were displayed in the original units. The effect sizes (e 2, ANOVA; Cohen' d, pairwise comparisons) as well as 95% confidence intervals (CI) were also calculated. Bivariate relationships were built with the help of Pearson correlation. The independent predictors were determined (independent variable, inflammatory parameters; independent variables, hormonally derived parameters, age, BMI) through a multiple linear regression. Significance at p<|human|>At p<|human|>At p<|human|>Significance of level p=0.05 (two tailed). Several comparison P values are adjusted.

RESULTS AND OBSERVATIONS:

Demographic and Clinical Characteristics

Demographic characteristics were similar. The mean ages of 30.2 + -6.1 years(controls), 25.8 +-2.9 years(PCOS 20-30) and 35.1 +-2.8 years(PCOS 30-40) were their mean ages. There was a mild body mass index (BMI) rise only in PCOS groups and was not statistically significant: 24.3+-3.2 kg/m2 (controls), 26.1+-4.5 kg/m2 (PCOS 20-30), 27.3+-5.1 kg/m2 (PCOS 30-40; ANOVA p=0.12; mean difference vs. controls 2.0 kg/m2, 95% CI [?]0.3-4.

Hormonal Profile Analysis

Statistical difference existed between the concentration of hormones in the control and PCOS groups (Table 1). There was a significant enhancement in the concentrations of luteinizing hormone among the PCOS (Heyward and Angelakis 20-30: 12.8+-3.4 IU/L; 30-40: 14.2+-3.8 IU/L; p< 0.001). No significant difference existed in FSH concentrations between groups (g=0.08). Control and PCOS had age gradual development of groups (controls: 165.2+-35.5 pg/mL; PCOS 20-30: 95.5+-30.2 pg/mL; PCOS 30-40: 82.1+-27.9 pg/mL). The progesterone level was significantly lower in the PCOS groups (controls 8.5 +-2.3 ng/mL; PCOS 20-30 3.1 +-1.0 ng/mL; p=0.001; PCOS 30-40 2.6 +-0.9 ng/mL). The elderly group (41.30ng/dl) demonstrated significant increases in testosterone of the PCOS group (20-30: 72.421.8ng/dl; 30-40: 79.621.1ng/dl).

Defects Inflammatory Analysis.

All indicators of inflammatory were enhanced immensely in subjects with PCOS as compared to the controls (Table 2). The age had distribution in the IL-6 levels (norm: 2.1+-0.9 pg/mL; PCOS 20-30: 4.8+-1.5 pg/mL; PCOS 30-40: 5.6+-1.7 pg/mL; p<0.001). Such as TNF-a also increased (control: 7.4+-2.8 pg/ml; PCOS 20-30: 12.3+-4.2 pg/ml; PCOS 30-40: 13.8+-4.6 pg/ml; p=0.001) and concentrations of hs-CRP rose directly with age in step-wise early increase in the three inflammatory markers in the PCOS populations.

Stratification Analysis Urban-Rural.

The urban residing subjects showed a significantly more significant concentration of inflammatory markers compared to the rural-residing ones in all PCOS subgroups (Table 3). IL-6 of PCOS urban residents of 20-30 years are higher as compared to rural inhabitants (5.2+-1.4 vs. 4.3+-1.2 pg/mL p=0.04 d=0.63). Urban residents were found to have higher TNF- a (13.1+-4.0 vs. 11. 2 -3.8 pg/mL; p=0.05; Cohen d= 0.47) and hs-CRP (4.5+-1.6 vs. 3.7+-1.5 mg/L; p=0.03; Cohen d= 0.52). The following were the general trends of the PCOS 30-40 years. These findings of the fact that it is possible to transplant urban-dwellers to explain the slightly increased inflammatory responses of the PCOS patients.

Correlation Analysis

The analysis of Pearson correlation showed that there were significant relationships between hormonal parameters and inflammatory markers (Table 4). IL-6 (r=0.58, p< 0.001), TNF- a (r=0.51, p<0.001) and hs-CRP (r=0.48, p<0.001) were positively related to testosterone. Estradiol on the other hand was also inversely correlated with IL-6 (r=[-#25 729, p<0.001), TNF-a (r=[-#45 408, p<0.001) and hs-CRP (r=[-#41 980, p<0.001]. LH had a positive though not significant correlation with hs-CRP (r=0.35, p=0.01). The results were strong within-group sensitivity assessment and partial correlations which controlled group membership (the complete results have been provided in Supplementary Table S1).

Multiple Linear Regression Analysis.

Inflammatory markers Studies involving hormonal parameters testosterone and estradiol concentration as dependent and independent (adjusted age and BMI wisely) variables, respectively, revealed that testosterone concentration was an independent positive predictor of IL-6 (b=0.48, p=0.001, 95% CI 0.21-0.75) and hs-CRP (b=0.35, p=0.008, 95% CI 0.10-0.60)

TABLE 1: Hormonal Profile Analysis

Parameter	Control (n=30)	PCOS 20–30 (n=30)	PCOS 30–40 (n=30)	p-value
LH (IU/L)	6.1 ± 2.0	12.8 ± 3.4*	14.2 ± 3.8*	<0.001
FSH (IU/L)	6.0 ± 1.5	5.3 ± 1.8	5.0 ± 1.6	0.08
17β-Estradiol (pg/mL)	165.2 ± 35.5	95.5 ± 30.2*	82.1 ± 27.9*	<0.001
Progesterone (ng/mL)	8.5 ± 2.3	3.1 ± 1.0*	2.6 ± 0.9*	<0.001
Testosterone (ng/dL)	41.3 ± 12.5	72.4 ± 18.9*	79.6 ± 21.1*	<0.001

Values are mean +- SD. P-values, one-way ANOVA; the values below 0.001 relative to control group (Bonferonni-adjusted post-hoc pairwise comparisons; adjusted a = 0.017).

TABLE 2: Inflammatory Markers

Marker	Control (n=30)	PCOS 20–30 (n=30)	PCOS 30–40 (n=30)	p-value
IL-6 (pg/mL)	2.1 ± 0.9	4.8 ± 1.5*	5.6 ± 1.7*	<0.001
TNF-α (pg/mL)	7.4 ± 2.8	12.3 ± 4.2*	13.8 ± 4.6*	<0.001
hs-CRP (mg/L)	1.8 ± 0.8	4.1 ± 1.7*	4.8 ± 1.9*	<0.001

Values are mean ± SD. Log-transformed prior to analysis; back-transformed results shown. P-values from one-way ANOVA; *p<0.001 compared to control group. Post-hoc Bonferroni corrected.

TABLE 3: Urban vs. Rural Stratification (PCOS Groups)

Marker	Urban PCOS 20–30 (n=10)	Rural PCOS 20–30 (n=10)	Urban PCOS 30–40 (n=10)	Rural PCOS 30–40 (n=10)	p-value
IL-6 (pg/mL)	5.2 ± 1.4	4.3 ± 1.2	5.9 ± 1.5	5.1 ± 1.4	0.04
TNF-α (pg/mL)	13.1 ± 4.0	11.2 ± 3.8	14.5 ± 4.5	13.2 ± 4.2	0.05
hs-CRP (mg/L)	4.5 ± 1.6	3.7 ± 1.5	5.2 ± 1.8	4.4 ± 1.6	0.03

Values are mean ± SD. P-values from independent samples t-tests comparing urban vs. rural within age strata. Effect sizes (Cohen's d) range 0.47–0.63.

TABLE 4: Correlation Tan - Hormonal Parameters and Inflammatory Markers.

Variables	IL-6	TNF-α	hs-CRP
Testosterone	r=0.58*	r=0.51*	r=0.48*
Estradiol	r=−0.52*	r=−0.45*	r=−0.41*
LH	r=0.22	r=0.18	r=0.35†
FSH	r=0.15	r=0.12	r=0.08
Progesterone	r=−0.31*	r=−0.26	r=−0.24

*p<0.001; †p=0.01. Pearson correlation coefficients. PCOS and control groups combined (n=90).

DISCUSSION

A combination of evidence of endocrine regulation induced by PCOS and associated with substantial rises in systemic inflammatory mediators is present in this study. The findings are consistent with other literature data and indicate the potential similarity between hormonal and immunological abnormalities in PCOS pathophysiology [2,4].

Hormonal Dysregulation: Pathophysiology.

The archetypal endocrinologic phenotype of raised LH, testosterone and reduced estradiol and progesterone is simple reproductive endocrinopathy in PCOS. LH increase is facilitated by the change in the gonadotropin releasing hormone (GnRH) pulsatility that is most likely due to the overstimulation of androgen-mediated feedback alteration at the hypothalamic-pituitary axis [1,3]. The high LH/FSH ratio is usually higher than 3:1 and encourages the androgen levels of the theca cells of the ovary to produce androgens, prevents the development of the follicles and estradiol secretion [3]. The gradual rise in the testosterone level in the older PCOS group might be indicative of either; a gradual rising androgen production by the ovary or similarly, a gradual reduction in metabolic clearance, over time. In case progesterone is significantly lacking then development of corpus luteum is impaired due to lack of ovulation [3].

Inflammatory Pathology and Risk of Cardiovascular Disease.

The significant increment in IL-6, TNF-a and hs-CRP is strong, which signifies a biologically significant finding. Interleukin (IL)-6 is an autocrine regulator of macrophage activation and a systemic stimulator of hepatic acute-phase atrophic proteins production [6,8]. Activated macrophages primarily express TNF-a and activate endothelial cells and activate the expression of adhesion molecules [8]. CRP is a prognostic indicator of the occurrence of cardiovascular events in the future beyond the influence of the conventional risk factors [9]. The combination of elevated levels of inflammatory markers may be reflective of the activation of innate immune pathways via a number of pathways. The hyperinsulinemia (present in the majority of PCOS patients) is directly capable of stimulating activation of the macrophages and generating pro-inflammatory cytokines [4]. Also, direct androgens may stimulate immune cell-mediated synthesis of inflammatory mediators [10].

Hormonal-Inflammatory Interactions

The positive relationship between androgen excess and immune activation has a strong positive relationship with all the inflammatory markers which is an indication of a mechanistic association between the two. Androgens have been shown to mediate the effect of

innate immune response through androgen receptor signaling in the immune cells through experimental studies [10]. The negatives correlation of estradiol and inflammatory indicators appears to be in line with established immunomodulatory results of estrogen that generally suppresses pro-inflammatory reactions [11]. Thus, it is possible that androgen excess with a relative insufficiency of estradiol in PCOS is a factor that contributes to unopposed pro-inflammatory effects [11].
Similarities between Environment and Lifestyle Factors
The observation that the urban home was connected to slightly greater concentrations of inflammatory markers in PCOS groups presents hint suggestion to the intervention of environmental and lifestyle variables in defining disease presenting characteristics. The contemporary lifestyle is defined by a variety of potentially pro-inflammatory exposures capable of operating on the inhabitants, which comprise ambient air pollution (particulate matter, nitrogen oxides), rising amounts of psychological stress, augmented job exposures and altered eating habits. Yet, these relations are observational, deductive; objective assessment of environmental exposures (particulate matter PM2.5 monitoring and dietary assessment tools and physical activity assessment tools through accelerometry) would be required to make inferences about causality and mechanism. It is one of the weaknesses of the study design. Notably, the urban-rural differences located were minimal (Cohen d 0.47-0.63), and have to be treated with care until they are repeated in other larger populations with more effectively characterized environment.

Age-Related Inflammatory Progression
The increasing levels of inflammatory markers of the older group of PCOS patients (30-40 years) than the younger group (20-30 years) indicate the presence of an inflammatory burden with a longer age and duration of developing the disease. This trend is aligned with the natural course of chronic inflammatory diseases, and, to some degree, this phenomenon may be the reason behind substantially higher cardiovascular risks in older PCOS patients [2].

Study Limitations
Various constraints are worth mentioning. The cross-sectional design does not allow establishing cause and effect relationships or time sequences. No cardiac autonomic indices (i.e. heart rate variability) were measured; consequently, autonomic dysregulation is an inferred process that needs direct measurements in future research. Markers of insulin resistance (HOMA-IR) and fasting glucose were not determined thus restricting the measurement of possible confounding by metabolic measures. The sample size, though sufficiently powerful to make primary comparisons, might not be as generalizable as possible. The characterization of environmental and lifestyle factors could have been improved with the help of the validated questionnaires on diet, physical activity, stress, and air quality exposure. The urban-rural stratification was done within the PCOS exclusively and could represent various unmeasured confounders such as occupational exposures, access to healthcare and socioeconomic status.

Study Strengths
The strengths involved the matched healthy control case-control design, concomitant measurement of several hormonal and inflammatory parameters, age and environmental residence stratification, and measurement in an understudied Arab population.

CONCLUSION

This study shows that women with PCOS have significant hormonal imbalances which are high levels of LH and testosterone with low levels of estradiol and progesterone. These hormonal disturbances are associated with a high level of systemic inflammatory markers (IL-6, TNF-a, hs-CRP), which indicates the presence of innate immune activation. There was positive correlation between inflammatory marker levels and androgens and negative correlation between inflammatory markers and estradiol which indicated possible mechanistic interactions. It is worth mentioning that the inflammatory markers showed a moderate increase among the urban PCOS patients and progressive increase as age advances, which should be investigated more.

These results can be used to support the conceptual framework that PCOS might be a systemic condition that integrates endocrine malregulation and immune activation-mechanisms which might be all combined to cause cardiovascular complications. Hormonal assessment and inflammatory assessment should be incorporated by the routine clinical assessment of PCOS patients, and it may help to identify people who are at a possibly increased risk of cardiovascular disease. Nevertheless, longitudinal studies involving direct measurement of autonomic functioning, full metabolic indicators (HOMA-IR, glucose patterns), and objective environment data are necessary to determine causality, predictive power, and mechanisms that can be corrected to develop intervention. This was a study that was done and reported based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

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Conflict of interest disclosure- child and parenting therapy sessions.

According to the authors, their involvement with this publication was not linked to a conflict of interest. Specifically:
* No researchers have received personally, in form of grants or financial incentives, any pharmaceutical companies, medical equipment manufacturers or commercial organizations that are in any way related to the current research.
* The author and the work have no personal, professional or financial relationship that can be perceived to bias or potentially bias the objectivity of this work.
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* All the authors have performed research design, data analysis, the interpretation and the preparation of the manuscript without any external influence.

DATA AVAILABILITY

The following research data that have been developed and computed could be availed at the request of the respective author in case it is reasonable. The data access is subject to the institutional data governance policies, the ethical approval provisions and data confidentiality of the participants. Request is a data codebook which involves all variables and measurement units and the coding rules.

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