
GYNAECOLOGY

Biochemical and Metabolic Disruptions in Endometriosis

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ABSTRACT

Objectives: Endometriosis is a chronic gynecological disorder characterized by endometrial glands and stroma outside the uterine cavity. This study aimed to characterize biochemical, hormonal, and inflammatory alterations in endometriosis, with the goal of gaining insights into disease mechanisms and exploring candidate biomarkers that could inform future studies on early diagnosis or targeted interventions.

Materials and Methods: A case-control study enrolled 300 participants aged 20 to 45 years, including 150 individuals diagnosed with endometriosis and 150 healthy controls recruited from hospitals across Thiruvananthapuram. Serum interleukin-6 (IL-6), prolactin, luteinizing hormone (LH), and follicle stimulating hormone (FSH) were measured using enzyme linked immunosorbent assay (ELISA), while triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH) were analyzed via chemiluminescent immunoassay (CLIA). Metabolic parameters were assessed using a semi-automated analyzer.

Results: Findings suggested that women with endometriosis had significantly higher body mass index (BMI), abdominal circumference, fasting blood sugar (FBS), triglycerides, low-density lipoprotein (LDL), IL-6, TSH, prolactin, and FSH, while high-density lipoprotein (HDL), T3, T4, and LH levels were lower ($p < 0.05$). Clinical conditions such as diabetes mellitus, dyslipidemia, thyroid disorders, polycystic ovarian syndrome (PCOS), and psychological

stress were more prevalent in cases. Receiver operating characteristic analysis identified prolactin and IL-6 as the strongest diagnostic predictors, while multivariable analysis confirmed body mass index, abdominal circumference, prolactin, and IL-6 as key factors associated with endometriosis.

Conclusion: This study revealed key biochemical and metabolic disruptions in endometriosis, linking obesity, PCOS, and stress to disease progression, and highlighted potential biomarkers for early diagnosis and targeted treatment.

Keywords: endometriosis, interleukin-6, metabolic disruptions, obesity, psychological stress.

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Introduction

Endometriosis, a systemic proinflammatory condition affecting 5–15% of women of reproductive age worldwide, is characterized by the ectopic growth of endometrial-like tissue outside the uterus, leading to dysmenorrhea, dyspareunia, and occasionally infertility⁽¹⁾. The development of endometriosis involves biochemical, endocrine, immune, and proinflammatory processes that interact with each other⁽²⁾.

Inflammation is a critical factor in the pathogenesis of endometriosis, driving cellular proliferation and tissue infiltration. Macrophages play a central role in this process, as their activation leads to the secretion of proinflammatory cytokines, which contribute to lesion progression and disease chronicity. Notably, cytokines such as interleukin (IL) (IL-6, IL-8, IL-33), nuclear factor kappa B (NF- κ B), and tumor necrosis factor-alpha (TNF- α) have been extensively studied for their involvement in various stages of endometriosis, facilitating inflammation, angiogenesis, and tissue remodeling⁽³⁾. IL-6, a pro-inflammatory cytokine, plays a significant role in the pathogenesis of endometriosis and has been suggested as a potential biomarker for its detection⁽⁴⁾.

Endometriosis is a hormone-dependent disorder involving endocrine dysfunction and multiple contributing factors⁽⁵⁾. Studies suggest a link between endometriosis and thyroid dysfunction, with an

increased risk of thyroid disease in affected individuals. Thyroid hormones may influence disease progression by modulating the immune response, activating neutrophils and macrophages, and creating a proinflammatory environment⁽⁶⁾. Elevated serum thyroid-stimulating hormone (TSH) or thyroxine (T4) levels have also been proposed as potential contributors to endometriosis development⁽⁷⁾. Key reproductive hormones follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin play crucial roles in the pathophysiology of endometriosis. Altered FSH and LH levels disrupt ovarian function, hormonal balance, and inflammation, promoting endometriosis progression, while prolactin, beyond lactation, contributes to menstrual irregularities, infertility, and cytokine-mediated inflammation. These hormones interact within the hypothalamic–pituitary–gonadal (HPG) axis, and dysregulation drives endometriosis progression^(8–10).

Apart from being a hormone-dependent and chronic disease, endometriosis also influences systemic metabolic indicators, including glucose and lipid metabolism⁽¹¹⁾. Recent research has increasingly emphasized the connection between metabolic status and endometriosis⁽¹²⁾. Women with endometriosis frequently exhibit lipid profile abnormalities, such as decreased high-density lipoprotein cholesterol (HDL-C) levels and elevated triglycerides (TG), total

cholesterol (TC), and LDL levels⁽¹³⁾. These findings highlight a strong link between lipid metabolism disorders and endometriosis, suggesting that lipid profiles could serve as accessible indicators and potential biomarkers for the disease⁽¹⁴⁾. In addition to lipid metabolism, glucose metabolism is also implicated in endometriosis. Elevated fasting blood sugar (FBS) levels suggest a potential link between glucose dysregulation and endometriosis, with a causal association reported in recent studies^(11, 15).

The pathophysiology of endometriosis extends beyond hormonal regulation, involving immune responses and metabolic dysregulation. This study delves into these interactions, highlighting body mass index (BMI), polycystic ovary syndrome (PCOS), and psychological stress as potential contributors to disease progression and identifying biomarkers for targeted intervention.

Materials and Methods

A case-control study aimed to investigate biochemical and metabolic disruptions associated with endometriosis. A total of 300 subjects were included, consisting of 150 endometriosis case subjects and 150 healthy controls. The participants were recruited from multiple reputed hospitals in Thiruvananthapuram like Credence Hospital, Pran Fertility and Well Woman Centre, polygenic risk score (PRS) Hospital Pvt Ltd, Yana Women's Hospital & Fertility Centre etc, in collaboration with Genetika, Centre for Advanced Genetic Studies, Thiruvananthapuram, where all laboratory investigations were performed.

In this study, the case group comprised clinically confirmed endometriosis subjects. For most cases, diagnosis was confirmed through laparoscopy, with histopathological evidence of endometrial glands and stroma located outside the uterine cavity. In instances where laparoscopy was not feasible, diagnosis was made based on transvaginal ultrasound (TVUS) performed by experienced gynecologists.

The exclusion criteria for cases included chronic metabolic or endocrine disorders, such as adrenal dysfunction or other significant hormonal abnormalities.

However, women with PCOS and thyroid dysfunction (hypothyroidism or hyperthyroidism) were included, as these conditions and their associated biochemical and metabolic markers were specifically evaluated in relation to endometriosis. PCOS was diagnosed based on the Rotterdam criteria, which require two of the following: oligo- or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasound, with other etiologies excluded.

Controls were defined as women with no clinical signs or history of endometriosis, including absence of chronic pelvic pain, dysmenorrhea, dyspareunia, or infertility. All controls underwent a clinical pelvic examination, and TVUS was performed by qualified gynecologists to exclude ovarian endometriomas or any ultrasound findings suggestive of endometriosis. Exclusion criteria for controls also included any prior diagnosis of endometriosis, known metabolic diseases, or ongoing hormone therapy.

Data collection included demographic factors and lifestyle factors. A detailed questionnaire was given to the case subjects and the healthy controls to acquire the demographic and lifestyle factors. After obtaining informed consent, 8-10 ml of fasting venous blood was collected from the subjects. Biochemical parameters including IL-6, prolactin, LH, and FSH were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits (Origin Diagnostics and Research, Kerala, India), following manufacturers protocols. Thyroid hormones (T3, T4, and TSH) were analyzed via clinical laboratory improvement amendments (CLIA) using Siemens Immulite 1000, India.

Metabolic parameters, including FBS, TC, TG, HDL, and LDL were measured using enzymatic colorimetric methods on a semi-automated clinical chemistry analyzer (Mispa neo, Agappe Diagnostics Ltd., India). Psychological stress was assessed using the Perceived Stress Scale (PSS-10), a 10-item self-report questionnaire that measures perceived levels of stress over the past month. A score > 20 was considered indicative of moderate to high stress.

A robust statistical framework was applied. Data were assessed for normality using the Shapiro-Wilk

test. Depending on data distribution, comparisons between cases and controls were performed using either independent t-tests for normally distributed variables or Mann–Whitney U tests for non-normally distributed variables. Descriptive statistics summarized data using means, standard deviations, and percentages. Diagnostic potential of biochemical markers was evaluated using receiver operating characteristic (ROC) curve analysis, reporting area under the curve (AUC) values, optimal cutoffs via the Youden Index, and additional metrics like sensitivity, and specificity. Multivariable logistic regression analysis was performed to identify independent factors associated with endometriosis. Variables included in the multivariable model were selected based on clinical relevance and significant differences observed in univariate analyses ($p < 0.05$). Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of associations. A p value < 0.05 indicated statistical significance. Data management was performed in Microsoft Excel, and analyses were

conducted using JAMOVI version 2.5.3.

Results

The study included 300 subjects, comprising 150 individuals with endometriosis (mean age: 34.9 ± 5.1 years) and 150 controls (mean age: 34.9 ± 6.3 years), all meeting the specified inclusion and exclusion criteria. The comparison of anthropometric, biochemical, and hormonal parameters between individuals with endometriosis and controls revealed significant differences in multiple variables. Cases exhibited higher abdominal circumference, weight, and BMI ($p = 0.001$). Metabolic markers, including FBS, TG, TC, and LDL were significantly elevated, while HDL was lower in cases ($p = 0.001$). Inflammatory marker IL-6 was markedly higher ($p = 0.001$). Thyroid function tests showed lower T3 and T4 but higher TSH in cases ($p = 0.001$). Reproductive hormone analysis indicated elevated FSH and prolactin levels, while LH was lower in cases ($p < 0.05$, t-test) (Table 1).

Table 1. Comparison of anthropometric, biochemical, and hormonal parameters between individuals with endometriosis and controls.

Parameter	Control Group (n = 150) Mean $\pm$ SD	Case Group (n = 150) Mean $\pm$ SD	t-value	p value
Age (years)	34.9 $\pm$ 6.3	34.9 $\pm$ 5.1	0.081	0.936
Abdominal Circumference (cm)	85.0 $\pm$ 12.6	95.9 $\pm$ 11.7	7.744	< 0.001
Height (cm)	155.6 $\pm$ 6.1	155.6 $\pm$ 6.1	2.140	0.033
Weight (kg)	57.2 $\pm$ 9.2	64.0 $\pm$ 10.6	5.961	< 0.001
BMI (kg/m ²)	23.6 $\pm$ 3.3	27.0 $\pm$ 4.2	7.860	< 0.001
Fasting blood sugar (FBS) (mg/dL)	89.5 $\pm$ 13.4	122.5 $\pm$ 42.7	9.035	< 0.001
Triglycerides (TG) (mg/dL)	117.3 $\pm$ 22.2	159.9 $\pm$ 39.3	11.547	< 0.001
Total cholesterol (TC) (mg/dL)	174.0 $\pm$ 32.5	231.5 $\pm$ 42.3	13.211	< 0.001
High-density lipoprotein (HDL) (mg/dL)	49.8 $\pm$ 6.7	42.8 $\pm$ 6.6	9.137	< 0.001
Low-density lipoprotein (LDL) (mg/dL)	100.8 $\pm$ 31.8	156.8 $\pm$ 36.8	14.109	< 0.001
Interleukin-6 (IL-6) (pg/mL)	3.18 $\pm$ 1.99	7.74 $\pm$ 5.13	10.152	< 0.001
Triiodothyronine (T3) (ng/dL)	118.6 $\pm$ 19.5	78.2 $\pm$ 21.9	16.890	< 0.001
Thyroxine (T4) (ng/dL)	7.73 $\pm$ 1.77	6.17 $\pm$ 2.44	6.340	< 0.001
Thyroid-stimulating hormone (TSH) (mIU/L)	2.40 $\pm$ 1.07	6.66 $\pm$ 4.04	12.512	< 0.001
Follicle-stimulating hormone (FSH) (mIU/L)	14.1 $\pm$ 5.7	15.9 $\pm$ 5.5	2.921	0.004
Luteinizing hormone (LH) (mIU/L)	13.9 $\pm$ 3.7	12.0 $\pm$ 5.8	3.339	< 0.001
Prolactin (ng/mL)	13.2 $\pm$ 5.4	27.3 $\pm$ 9.5	15.773	< 0.001

The study revealed significant differences in the prevalence of various clinical conditions between the control and case groups (Table 2). Diabetes was more prevalent in the case group (16.7%) compared to the control group (3.3%) with a statistically significant difference ($\chi^2 = 14.8$, $p = 0.001$). Similarly, dyslipidemia was more common in the case group (17.3%) compared to the control group (6%) ($\chi^2 = 9.35$, $p = 0.002$). A significantly higher incidence of

thyroid disorders was observed in the case group (23.3%) compared to the control group (4.7%) ($\chi^2 = 21.7$, $p = 0.001$). Psychological stress was more prevalent in the case group (18.7%) than in the control group (8.7%) ($\chi^2 = 6.36$, $p = 0.012$). Additionally, the prevalence of PCOS was higher in the case group (18%) compared to the control group (7.3%) ($\chi^2 = 7.71$, $p = 0.005$). All differences were statistically significant, with p values less than 0.05.

Table 2. Association of various clinical variables between the case and control group.

Comorbidity	Group	n (%)	χ^2	df	p value
Diabetes	Control	5 (3.3%)	14.8	1	0.001
	Case	25 (16.7%)			
Dyslipidemia	Control	9 (6.0%)	9.35	1	0.002
	Case	26 (17.3%)			
Thyroid Disorder	Control	7 (4.7%)	21.7	1	0.001
	Case	35 (23.3%)			
Psychological Stress	Control	13 (8.7%)	6.36	1	0.012
	Case	28 (18.7%)			
PCOS	Control	11 (7.3%)	7.71	1	0.005
	Case	27 (18.0%)			

PCOS: polycystic ovarian syndrome

The ROC curve demonstrates the diagnostic ability of the test, with the AUC indicating its overall accuracy. A higher AUC value suggests better test performance, with values closer to 1.0 representing excellent diagnostic ability (Fig. 1). Prolactin demonstrated the highest diagnostic performance with a significantly high AUC, making it the most reliable predictor for distinguishing between cases and controls. IL-6 was identified as a strong predictor, showing a bowed ROC curve towards the top-left corner, indicating excellent diagnostic accuracy. TSH also performed well, exhibiting a high AUC, suggesting it is a good predictor, though not as exceptional as Prolactin. T3 and FSH demonstrated moderate diagnostic performance, with AUC values above 0.5, indicating results better than random chance. In contrast, LH and T4 showed moderate diagnostic accuracy, with their

ROC curves positioned above the diagonal but not exhibiting the same level of precision as the strongest predictors.

In this study, several factors were associated with the case group (Table 3). Diabetes, dyslipidemia, thyroid disorder, and PCOS showed significant associations in the univariable analysis, but many lost significances in the multivariable analysis. Abdominal circumference (≥ 88 cm) and BMI (≥ 25 kg/m²) were strongly associated with the case group, with both univariable and multivariable analyses showing significant results. High levels of LH, FSH, prolactin, and IL-6 were also significantly associated with the case group, with prolactin and IL-6 showing strong associations in both analyses. Other variables, including lipid parameters and thyroid hormones, did not remain significant after adjustment.

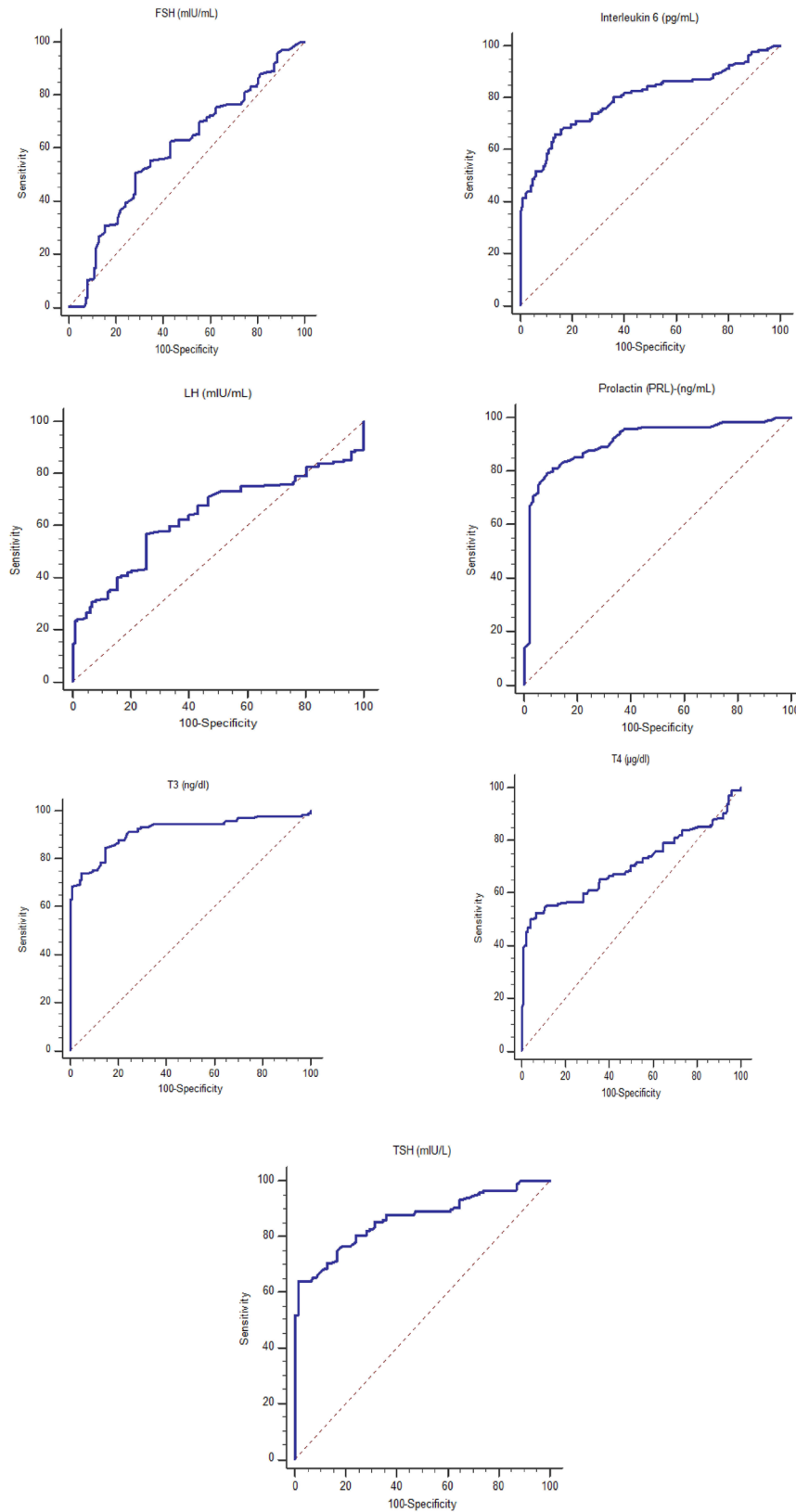


Fig. 1. Receiver operating characteristic curve of various parameters

Table 3. Association of demographic, biochemical, and hormonal factors with case group in univariable and multivariable analyses.

Parameter	Control Group (n = 150) Mean ± SD	Case Group (n = 150) Mean ± SD	t-value	p value	OR (univariable)	OR (multivariable)
Diabetes	No	145 (96.7)	125 (83.3)	< 0.001	Ref	Ref
	Yes	5 (3.3)	25 (16.7)		5.80 (2.33-17.59, p < 0.001)	0.33 (0.02-5.09, p = 0.416)
Dyslipidemia	No	141 (94.0)	124 (82.7)	0.004	Ref	Ref
	Yes	9 (6.0)	26 (17.3)		3.28 (1.53-7.67, p = 0.003)	2.38 (0.23-23.46, p = 0.448)
Thyroid Disorder	No	143 (95.3)	115 (76.7)	< 0.001	Ref	Ref
	Yes	7 (4.7)	35 (23.3)		6.22 (2.82-15.74, p < 0.001)	7.59 (0.67-124.60, p = 0.123)
PCOS	No	139 (92.7)	123 (82.0)	0.009	Ref	Ref
	Yes	11 (7.3)	27 (18.0)		2.77 (1.35-6.05, p = 0.007)	1.37 (0.19-10.59, p = 0.755)
Abdominal circumference	< 88 cm	100 (66.7)	29 (19.3)	< 0.001	Ref	Ref
	≥ 88 cm	50 (33.3)	121 (80.7)		8.34 (4.98-14.35, p < 0.001)	17.14 (3.80-107.99, p = 0.001)
BMI	< 25	107 (71.3)	52 (34.7)	< 0.001	Ref	Ref
	≥ 25	43 (28.7)	98 (65.3)		4.69 (2.90-7.70, p < 0.001)	16.59 (2.81-167.11, p = 0.006)
LH	> 12.25 (mIU/mL)	112 (74.7)	65 (43.3)	< 0.001	Ref	Ref
	≤ 12.25 (mIU/mL)	38 (25.3)	85 (56.7)		3.85 (2.38-6.34, p < 0.001)	1.64 (0.41-6.81, p = 0.484)
FSH	≤ 15.86 (mIU/mL)	108 (72.0)	74 (49.3)	< 0.001	Ref	Ref
	> 15.86 (mIU/mL)	42 (28.0)	76 (50.7)		2.64 (1.64-4.29, p < 0.001)	1.71 (0.37-8.11, p = 0.489)
Prolactin	≤ 18.2 (ng/mL)	134 (89.3)	28 (18.7)	< 0.001	Ref	Ref
	> 18.2 (ng/mL)	16 (10.7)	122 (81.3)		36.49 (19.34-72.92, p < 0.001)	124.16 (21.51-1346.30, p < 0.001)
IL-6	≤ 5.57 (pg/mL)	130 (86.7)	51 (34.0)	< 0.001	Ref	Ref
	> 5.57 (pg/mL)	20 (13.3)	99 (66.0)		12.62 (7.20-23.02, p < 0.001)	7.91 (1.30-62.44, p = 0.032)

OR: odds ratio, PCOS: polycystic ovarian syndrome, BMI: body mass index, LH: luteinizing hormone, FSH: follicle-stimulating hormone, IL: interleukin

Discussion

Endometriosis cases exhibited higher BMI, abdominal circumference, and metabolic disturbances, including elevated FBS, TG, and LDL, with lower HDL (p = 0.001). IL-6, prolactin, and FSH were significantly higher, while LH was lower. Diabetes, dyslipidemia, thyroid disorders, stress, and PCOS were more prevalent in cases. Prolactin was the strongest predictor, followed by IL-6 and TSH.

Malvezzi et al emphasized the multifactorial nature of endometriosis and the challenges in modeling its pathology due to the lack of reliable animal models. They highlighted the need for novel research approaches, including artificial intelligence, three-dimensional cultures, and organ-on-chip models, to enhance understanding and improve treatment strategies. Their work focused on advancing

experimental models to study endometriosis and assess drug efficacy⁽¹⁶⁾.

In contrast, the present study directly investigated the metabolic, hormonal, and inflammatory alterations associated with endometriosis, providing clinical insights that bridge gaps in understanding disease pathophysiology. This study identified significant metabolic imbalances, including elevated FBS, TG, LDL, and reduced HDL (Table 1). Additionally, the findings highlighted the role of adiposity through increased BMI and abdominal circumference. Notably, prolactin emerged as the most potent diagnostic marker, followed by IL-6, reinforcing the inflammatory component of endometriosis (Fig. 1). Furthermore, the study established a link between thyroid dysfunction (elevated TSH, reduced T3 and T4) and endometriosis, along with a higher prevalence of

PCOS, suggesting overlapping endocrine and metabolic mechanisms.

By focusing on clinically measurable metabolic, hormonal, and inflammatory parameters, the present study addressed a critical gap left by previous researchers who primarily focused on experimental modeling rather than direct clinical and biochemical associations. These findings provided valuable diagnostic and pathophysiological insights, emphasizing the need for an integrated approach to managing endometriosis beyond current experimental models⁽¹⁶⁾.

Just like any other study, the present study had its limitations. Selection bias may exist due to hospital-based recruitment, limiting generalizability. Self-reported demographic and lifestyle data introduced the risk of recall bias. While key biochemical markers were analyzed, other relevant inflammatory markers were not included. Variability in diagnosis, with some cases relying on imaging rather than laparoscopy, may affect consistency. Despite a robust sample size, more extensive multi-center studies are needed for broader validation. Another limitation of this study was that although hormonal assays were performed, the timing of blood sampling during the menstrual cycle was not uniformly standardized across all participants. As levels of FSH and LH fluctuate significantly throughout the menstrual cycle, this may have contributed to variability and potentially higher observed values in both cases and controls. Finally, this case-control study was the potential presence of confounding factors influencing biochemical and hormonal measurements. Although multivariable analysis was performed to adjust for key confounders, residual confounding cannot be entirely excluded.

The most notable findings of the present study were the significant metabolic, hormonal, and inflammatory alterations observed in individuals with endometriosis. Cases exhibited elevated FBS, TG, and LDL levels, along with reduced HDL, indicating a metabolic imbalance (Table 1). Higher BMI and abdominal circumference further reinforced the role of adiposity in disease pathology. Notably, prolactin

demonstrated the highest diagnostic accuracy, followed by IL-6, highlighting the inflammatory component of endometriosis (Fig. 1). Thyroid dysfunction, characterized by elevated TSH and reduced T3 and T4 levels, was significantly associated with endometriosis, suggesting an endocrine-metabolic link. Additionally, the increased prevalence of PCOS in cases indicated shared pathophysiological mechanisms between the two conditions.

These findings aligned with previous research indicating an unfavorable lipid profile in women with endometriosis. One study reported higher LDL, non-HDL, TG, and TC levels, along with a lower HDL:TC ratio, in the endometriosis group compared to controls⁽¹⁷⁾. Similarly, other studies identified a link between elevated serum TG and an increased risk of endometriosis, as well as significantly lower HDL-C and higher LDL-C levels in affected individuals^(18,19). These findings suggested that metabolic dysregulation may play a crucial role in the pathophysiology of endometriosis, potentially contributing to disease progression through mechanisms involving inflammation and hormonal imbalances.

Another key metabolic alteration observed in the present study was the elevation of FBS levels in individuals with endometriosis, indicating a potential link between glucose metabolism and disease pathology (Table 1). These findings aligned with previous research that reported a significantly higher triglyceride-glucose (TyG) index in women with endometriosis compared to those without the condition, reinforcing the association between insulin resistance and endometriosis⁽²⁰⁾. Furthermore, earlier studies supported significant causal associations between type 1 diabetes mellitus (T1DM), gestational diabetes mellitus (GDM), and fasting insulin (FI) levels in relation to endometriosis⁽¹⁵⁾. Endometriosis patients demonstrated elevated insulin (INS) levels [6.90 (5.10–9.50) vs. 6.50 (4.80–8.90) μ U/mL, $p = 0.005$], further indicating a state of insulin resistance⁽¹¹⁾. These observations suggested that metabolic dysfunction, particularly alterations in glucose homeostasis, played a crucial role in the pathophysiology of endometriosis.

The present study supports previous research that has reported elevated IL-6 levels in individuals with endometriosis, reinforcing its role in disease pathology^(21,22). In addition to confirming these findings, the current study identified IL-6 as one of the strongest diagnostic markers, with significant associations observed in univariable and multivariable analyses (Table 3, Fig. 1). This highlights the clinical relevance of IL-6 in endometriosis and suggests its potential utility as a biomarker for disease diagnosis and progression assessment.

The present study identified prolactin as the most potent diagnostic marker for endometriosis, as shown in Fig. 1. This finding was consistent with previous research that has reported elevated serum prolactin levels in individuals with endometriosis⁽²³⁾. Moreover, earlier studies have demonstrated the diagnostic utility of prolactin when assessed alongside CA-125. For instance, one study found that combining serum CA-125 (cut-off: 19.9 U/L) and prolactin (cut-off: 14.8 ng/ml) enabled the diagnosis of peritoneal endometriosis with 77% sensitivity, 88% specificity, and a high negative predictive value of 97%⁽²⁴⁾. However, it is important to note that the current study did not evaluate other potential causes of hyperprolactinemia, such as pituitary adenomas or the use of medications that influence prolactin levels. As such, the interpretation of prolactin as a diagnostic marker should be made with caution, and further studies are needed to validate these findings while controlling for these confounding variables.

The present study identified significant hormonal alterations in individuals with endometriosis compared to controls. Elevated FSH levels and reduced LH levels were observed in the case group, suggesting disruptions in ovarian function. Additionally, thyroid dysfunction was more prevalent among cases, characterized by lower T3 and T4 levels and elevated TSH levels (Table 1). These findings indicated a potential link between hormonal dysregulation and endometriosis pathophysiology. Previous studies have reported similar patterns of hormonal imbalance in endometriosis. One study

found significantly higher FSH levels in individuals with endometriosis than controls, supporting the current study's findings⁽²⁵⁾. Another reported decreased LH levels in affected individuals, consistent with the present results⁽²⁶⁾. Regarding thyroid dysfunction, one group highlighted upregulated TSH receptors in ectopic endometrial tissue and elevated TRAb IgG levels in endometriosis patients, suggesting an overlap in pathophysiology⁽⁷⁾. Additionally, a higher prevalence of hypothyroidism was observed in women with endometriosis (9.6% vs 1.5%, $p < 0.0001$), reinforcing the association between thyroid dysfunction and endometriosis⁽²⁷⁾. These comparisons suggest that hormonal alterations may be critical in the disease's development and progression, warranting further investigation into their clinical implications.

In the present study, individuals with endometriosis exhibited higher BMI and abdominal circumference, as outlined in Table 1. Existing research suggests a correlation between BMI and endometriosis. For example, one study reported a significant association between elevated BMI and endometriosis⁽²⁸⁾. Similarly, another study observed a higher incidence of endometriosis in obese women ($\text{BMI} > 27.50 \text{ kg/m}^2$) compared to those with normal weight⁽²⁹⁾. These findings align with the present study, reinforcing the association between increased BMI and endometriosis.

PCOS was significantly associated with endometriosis in the current study (Table 2, Table 3), aligning with previous research that supports this link. A case-control study reported a significant association between endometriosis and PCOS in women presenting with pelvic pain and/or infertility⁽³⁰⁾. Additionally, recent findings highlighted a genetic correlation and shared risk genes between these conditions, further reinforcing the potential interplay of genetic factors in their coexistence⁽³¹⁾.

The significantly higher prevalence of psychological stress in the case group (18.7%) compared to the control group (8.7%) ($\chi^2 = 6.36$, $p = 0.012$) indicated a strong association between

endometriosis and increased stress levels, as shown in Table 2. This finding suggests that individuals with endometriosis may experience elevated stress due to factors such as chronic pelvic pain, infertility concerns, and the overall burden of managing a chronic condition. Psychological stress has been recognized as a contributing factor in the progression and symptom severity of endometriosis, potentially exacerbating inflammatory responses and pain perception. Clinical studies have consistently demonstrated that endometriosis is associated with high levels of chronic stress, reinforcing the need for a multidisciplinary approach to management that includes psychological support alongside conventional medical and surgical treatments^(32, 33).

This study underscored the multifactorial nature of endometriosis, revealing significant metabolic, hormonal, and inflammatory alterations in affected individuals. Identifying prolactin as the most potent predictive marker and IL-6 and thyroid dysfunction expands the diagnostic landscape for endometriosis. The findings emphasized the association between metabolic dysregulation and endometriosis, reinforcing the need for a comprehensive, interdisciplinary approach to disease management. Additionally, the observed overlap with PCOS and increased psychological stress further supports a shared pathophysiological basis among endocrine disorders.

Unlike prior research focused on infertility and pelvic pain, it expands the scope by linking endometriosis to metabolic syndrome, psychological stress, and endocrine dysfunction. Strengthening the case for prolactin and IL-6 as diagnostic biomarkers beyond CA-125, the findings advocate for a multidisciplinary approach. Given the limitations of hospital-based recruitment and the need for broader validation, future multi-center studies with a larger sample size should further explore the identified metabolic, endocrine, and inflammatory associations. These findings contributed to a better understanding of the systemic nature of endometriosis, paving the way for more targeted diagnostic and therapeutic

strategies beyond traditional gynecological approaches.

Conclusion

Endometriosis is a multifaceted disorder involving chronic inflammation, hormonal imbalances, and metabolic dysfunction. This study reinforces the systemic nature of the disease by demonstrating key associations between endocrine disturbances, proinflammatory markers, and metabolic alterations. Notably, prolactin and IL-6 emerged as potential diagnostic indicators, highlighting their clinical utility. The observed interplay between immune, metabolic, and endocrine pathways underscores the importance of an integrated, multidisciplinary approach for effective diagnosis and management. Future large-scale, multi-center studies are essential to validate these findings and guide personalized therapeutic strategies.

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Authors contribution

D.S.: conceptualization, data curation, formal analysis, investigation, methodology, resources, visualization, writing – original draft;

N.M.: conceptualization, methodology, resources, supervision, writing – review & editing;

D.R.D.: conceptualization, project administration, supervision, writing – review & editing;

B.J.: data curation, investigation;

J.V.C.: data curation, investigation;

S.M.J.: data curation, investigation;

S.K.: data curation, investigation;

P.R.: data curation, investigation;

A.S.: methodology, validation;

P.M.L.: validation.

Potential conflicts of interest

The authors declare no conflicts of interest.

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