Evaluation of angiopoietin-like protein 4 levels in patients with endometriosis

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Abstract

Objective: Endometriosis is a chronic inflammatory disorder lacking definitive laboratory diagnostic markers. Angiopoietin-like protein-4 (ANGPTL4) is a protein involved in the regulation of angiogenesis and inflammation. The aim of the present study was to evaluate serum and peritoneal fluid (PF) levels of ANGPTL4 to explore its potential role in the pathogenesis of endometriosis.

Material and Methods: This prospective study included women with surgically confirmed endometriosis and age-matched healthy controls with similar demographic characteristics. Clinical and laboratory parameters, including serum ANGPTL4, anti-Müllerian hormone (AMH), and cancer antigen-125 (CA125) levels were compared between groups. In addition, PF ANGPTL4 levels were assessed in the endometriosis group.

Results: Serum ANGPTL4 (512.65±46.91 vs. 177.60±11.84 ng/mL, $p<0.001$) and CA125 (53.52±6.05 vs. 20.10±3.18 U/mL, $p<0.001$) levels were significantly higher in endometriosis group. Serum ANGPTL4 positively correlated with the severity of pelvic pain and dyspareunia, serum CA125 level and PF ANGPTL4, and negatively correlated with AMH ($r=0.743$, $p<0.001$; $r=0.624$, $p<0.001$; $r=0.444$, $p<0.001$; $r=0.841$, $p<0.001$; and $r=-0.380$, $p<0.001$, respectively). Receiver operating characteristic analysis identified an optimal serum ANGPTL4 cut-off value of 188.61 ng/mL (area under the curve =0.755, sensitivity 75% and specificity 62.5%, positive predictive value 66.7%, and negative predictive value 71.4%).

Conclusion: Serum ANGPTL4 levels were significantly higher in women with endometriosis and were associated with clinical and laboratory parameters. It may serve as a supportive biomarker in the clinical assessment of endometriosis. [J Turk Ger Gynecol Assoc. 2026; 27(3): 203-10]

Keywords: Anti-Müllerian hormone, angiopoietin-like protein 4, CA125 antigen, endometriosis, pelvic pain

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Introduction

Endometriosis is a chronic, progressive disease characterized by local and systemic inflammation and the presence of ectopic endometrial tissue (1,2). Ectopic endometrial implants are most frequently observed in the ovaries, as well as in extraovarian pelvic peritoneal locations, including the broad ligament, pouch of Douglas, and uterosacral ligaments (2,3). Endometriosis is clinically diagnosed in approximately 10% of women of reproductive age. Its most common manifestations include infertility and pain-related symptoms, particularly dysmenorrhea and chronic pelvic pain, which have been shown to markedly reduce quality of life (1,2).

Currently, no biomarker has demonstrated sufficient accuracy to serve as a standalone diagnostic tool for endometriosis (4). The clinical value of cancer antigen-125 (CA125) for diagnosing endometriosis is restricted because elevated levels can occur in ovarian, bladder, and renal cancers, as well as in inflammatory disorders and adenomyosis (5). Surgery remains the gold standard for the diagnosis of endometriosis (3). Therefore, research efforts have increasingly focused on developing non-invasive diagnostic methods suitable for clinical use.

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Although the pathogenesis of endometriosis has not been fully elucidated, angiogenesis, inflammation, oxidative stress, and fibrosis are recognized as central mechanisms (2). Angiopoietin-like protein 4 (ANGPTL4), a member of the angiopoietin-like family, is involved in the regulation of inflammation and angiogenesis (6). However, the role of ANGPTL4 in the pathophysiology and clinical significance of endometriosis remains insufficiently understood. The revised American Society for Reproductive Medicine (rASRM) classification is the most widely used surgical staging system for endometriosis and remains the standard method for assessing disease extent despite its limited correlation with symptom severity (7,8). Whether circulating and local ANGPTL4 levels vary according to disease stage has not yet been investigated. Given this context, the current study aimed to investigate whether serum levels of ANGPTL4 may have potential value in the clinical evaluation of women with endometriosis compared with a healthy control group. In addition, peritoneal fluid (PF) ANGPTL4 levels were evaluated in the endometriosis group for a better understanding of local factors. Furthermore, serum and PF ANGPTL4 levels were evaluated according to rASRM stage to explore their association with disease severity.

Material and Methods

Study population

The study was approved by Ankara Bilkent City Hospital Ethics Committee (approval no: TABED 1-25-1372, date: 04.06.2025) and National Institutes of Health Clinical Trial's Registry (#NCT07164196).

After detailed information about the study protocol was provided, written informed consent was obtained from all participants.

Exclusion criteria for both the endometriosis and control groups included postmenopausal status, a history of previous surgery for endometriosis, adenomyosis, infectious or acute/chronic inflammatory diseases, autoimmune disorders, tumor history, menorrhagia or hypermenorrhea, pregnancy, lactation, use of intrauterine devices, and any medical treatment, including hormonal therapy or antidiabetic medications.

Data collection and evaluation of ANGPTL4 levels

Demographic characteristics and clinical findings, including body mass index (BMI), serum CA125 levels, serum anti-Müllerian hormone (AMH) levels, pelvic pain, and dyspareunia were recorded for all participants. Serum ANGPTL4 levels were compared between the endometriosis patients and the healthy controls. The PF ANGPTL4 levels were also evaluated, but only in women with endometriosis.

Dyspareunia was defined as recurrent or persistent pain associated with sexual intercourse which causes distress, including the complaints during or within 24 hours after the intercourse (9). Pelvic pain was defined as cyclic or non-cyclic lower abdominal pain for at least six months, unrelated to pregnancy (10). Visual analogue scale (VAS) for pain, with possible scores from 0 to 10, was applied to investigate the presence and severity of both pelvic pain and dyspareunia. The 0 point was assessed as having no pain, whereas the 10 point was assigned to the worst pain the patient had experienced (11).

The blood serum was analyzed to observe systemic ANGPTL4 levels, and the PF was analyzed for the local ANGPTL4 levels in pelvic peritoneum. Blood sampling from antecubital vein after eight hours fasting was performed to obtain serum samples. The PF samples were taken at the begining of the laparoscopic procedure just after the insertion of the first lateral trochar into the peritoneal cavity. The peripheral venous blood serum and PF samples were centrifuged at 2500 rpm for 15 min. All the collected samples were stored at -80 °C in aliquots and the ANGPTL4 levels were analyzed at once. The ANGPTL4 levels were determined using an enzyme-linked immunosorbent assay (ELISA) kit (catalog no. E3119Hu/Bioassay Technology Laboratory, Shanghai, China) by quantitative sandwich ELISA. The absorbance values were read at 450 nm using Thermo Scientific Multiskan GO spectrophotometer (Thermo Fisher Scientific, USA). The assay sensitivity (minimum detectable concentration) was 12.5 ng/mL. The intra-assay and inter-assay coefficients of variation (CVs) were <10%.

Statistical analysis

Statistical Package for the Social Sciences, v27.0 for Windows (SPSS Inc., Chicago, IL, USA) was used in statistical analyses. Categorical variables were compared using Pearson's chi-square test. Fisher's exact test was used when the assumptions for the chi-square test were not met. The normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous variables are expressed as mean ± standard deviation and compared using Student's t-test, whereas non-normally distributed variables are expressed as median (minimum-maximum) and analyzed using the Mann-Whitney U test. A post-hoc power analysis was performed using G*Power version 3.1 (Heinrich Heine University, Düsseldorf, Germany) for the primary outcome (serum ANGPTL4 levels) based on a two-tailed independent samples t-test. The analysis assumed an effect size of Cohen's d=1.8, an alpha level of 0.05, and the observed group sizes (n=40 per group). The achieved statistical power was >0.99.

Spearman's rank correlation analysis was performed to assess the relationships between serum and PFANGPTL4 levels and

clinical and biochemical variables. Furthermore, to determine whether ANGPTL4 levels were independently associated with disease severity after adjustment for potential confounding factors, separate multivariable linear regression analyses were performed for serum and PFANGPTL4 levels in the endometriosis group. Patients with endometriosis were further stratified according to rASRM stage (stage III and stage IV), and serum and PFANGPTL4 levels were compared between the two groups. Disease stage (rASRM), infertility, serum AMH, and serum CA125 were entered simultaneously into the models using the enter method. Multicollinearity was assessed using variance inflation factors, and values <2 were considered indicative of the absence of significant multicollinearity.

To evaluate whether serum ANGPTL4 was independently associated with the presence of endometriosis, a multivariable binary logistic regression analysis was performed with endometriosis status (case/control) as the dependent variable. Serum ANGPTL4, serum CA125, serum AMH, and infertility status were entered simultaneously as independent variables using the enter method. These covariates were selected based on their clinical relevance and their potential to confound the association between serum ANGPTL4 and the presence of endometriosis. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of serum ANGPTL4, and the area under the curve (AUC), optimal cut-off value, sensitivity, and specificity were determined. To evaluate the incremental diagnostic value of serum ANGPTL4 beyond CA125, a binary logistic regression model was constructed with endometriosis status as the dependent variable and serum CA125 and serum ANGPTL4 levels as independent variables. Predicted probabilities from this model were used to generate the combined CA125-ANGPTL4 ROC curve. ROC curves were also generated separately for serum CA125 and serum ANGPTL4. The AUCs and their 95% CIs were calculated, and the AUC of the combined model was compared with that of CA125 alone using the non-parametric DeLong test for correlated ROC curves. A p-value of <0.05 was considered statistically significant.

Results

A total of 92 women of reproductive age were enrolled. After the relevant exclusions as shown in the flow diagram (Figure 1), 80 participants remained in final analysis, consisting of 40 women who underwent laparoscopic surgery and received a confirmed diagnosis of endometriosis and the control group of 40 women. Clinical characteristics, demographic data and ANGPTL4 levels are shown in Table 1. Serum ANGPTL4, CA125 levels, pelvic pain scores, and dyspareunia scores were significantly increased in the endometriosis group ($p<0.001$), whereas serum AMH levels were significantly decreased in the endometriosis group ($p<0.001$) (Table 1).

Spearman's correlation analysis revealed significant and strong association between the serum and PF levels of ANGPTL4 ($r=0.841$, $p<0.001$). Serum AMH levels were negatively correlated with serum and PF ANGPTL4 levels and with serum CA125 levels ($r=-0.380$, $p<0.001$; $r=-0.370$, $p=0.019$; $r=-0.298$, $p=0.007$, respectively). ANGPTL4 levels were significantly correlated with serum CA125 levels, as well as with pelvic pain and dyspareunia VAS scores ($p<0.05$), as presented in Table 2.

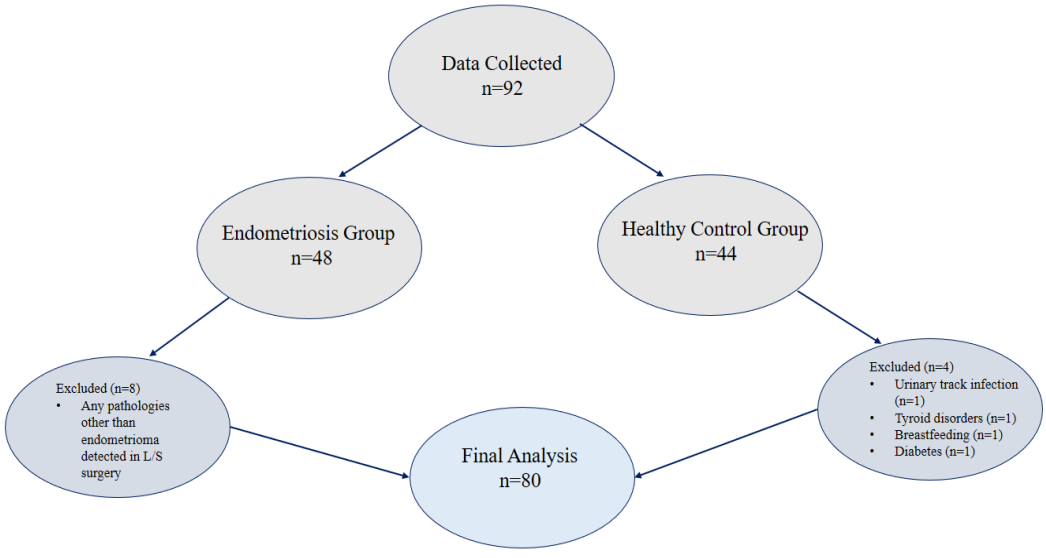

Figure 1. Flow diagram of the study
L/S surgery: Laparoscopic surgery

A multivariable binary logistic regression analysis was performed to determine whether serum ANGPTL4 was independently associated with the presence of endometriosis after adjustment for serum CA125, serum AMH, and infertility status. The overall model was significant (Omnibus test, χ^2=57.906, p<0.001) and demonstrated good calibration (Hosmer-Lemeshow test, χ^2=10.215, p=0.250). The Nagelkerke R^2 was 0.687. Serum ANGPTL4 was not independently associated with endometriosis after adjustment for serum CA125, serum AMH, and infertility status (adjusted OR =1.003, 95% CI: 0.998-1.009, p=0.235), whereas serum CA125 was the only variable that remained significantly associated with endometriosis (adjusted OR=1.081, 95% CI: 1.017-1.148, p=0.012).

The ROC analysis demonstrated that serum ANGPTL4 had a statistically significant ability to discriminate women with endometriosis from controls (AUC =0.755, 95% CI: 0.648-0.862; p<0.001). At the optimal cut-off value of 188.61 ng/mL, serum ANGPTL4 showed a sensitivity of 75% and a specificity of 62.5%, with a positive predictive value of 66.7% and a negative predictive value of 71.4% (Table 3). Serum CA125 also demonstrated significant discriminatory ability for endometriosis, with an AUC of 0.888 (95% CI, 0.815-0.962; p<0.001). To further evaluate the incremental diagnostic value of serum ANGPTL4 beyond CA125, a combined model incorporating serum CA125 and serum ANGPTL4 was evaluated. The combined model demonstrated a higher AUC of 0.931 (95% CI, 0.879-0.982; p<0.001) than CA125 alone. The difference between the AUCs of serum CA125 alone and the combined CA125-ANGPTL4 model was statistically significant according by the DeLong test (difference in AUC, 0.051; 95% CI, 0.003-0.099; p=0.037), indicating significantly improved discriminatory performance with the addition of serum ANGPTL4. The ROC characteristics of the individual biomarkers and the combined model are presented in Table 3 and Figure 2.

Table 1. Sociodemographic characteristics and clinical findings of the participants

	Endometriosis group (n=40)	Control group (n=40)	p-value
Age† years	33.72±1.05	36.19±1.19	0.624
BMI† kg/m²	25.95±0.89	25.08±1.64	0.628
Pelvic pain VAS‡ 0-10 points	6 (3-8)	2 (2)	<0.001*
Dyspareunia VAS‡ 0-10 points	4 (3-7)	2 (2.25)	<0.001*
AMH† ng/mL	1.39±0.23	1.81±0.42	<0.001*
Serum CA125† U/mL	53.52±6.05	20.10±3.18	<0.001*
ANGPTL4 serum† ng/mL	512.65±46.91	177.60±11.84	<0.001*
ANGPTL4 PF ng/mL	314.76±15.17	N/A	N/A

*p-value <0.05 is considered as statistically significant. †: Student's t-test, ‡: Mann-Whitney U test. ANGPTL4 PF levels were measured only in the endometriosis group. N/A: Non-applicable, BMI: Body mass index, VAS: Visual analogue scale, AMH: Anti-Müllerian hormone, CA125: Cancer antigen-125, ANGPTL4: Angiopoietin-like protein-4, PF: Peritoneal fluid

Table 2. Correlation analysis between ANGPTL4 levels and clinical and laboratory parameters in women with endometriosis

		ANGPTL4 PF	ANGPTL4 serum	Dyspareunia	Pelvic pain	AMH	CA125
CA125	r	0.387	0.444	0.588	0.594	-0.298	N/A
	p-value	0.014*	<0.001*	<0.001*	<0.001*	0.007*	N/A
AMH	r	-0.370	-0.380	-0.509	-0.399	N/A	
	p-value	0.019*	<0.001*	<0.001*	<0.001*	N/A	
Pelvic pain	r	0.548	0.743	0.764	N/A		
	p-value	<0.001*	<0.001*	<0.001*	N/A		
Dyspareunia	r	0.452	0.624	N/A			
	p-value	0.004*	<0.001*	N/A			
ANGPTL4 serum	r	0.841	N/A				
	p-value	<0.001*	N/A				
ANGPTL4 PF	r	N/A					
	p-value	N/A					

*p-value <0.05 is considered as statistically significant. N/A: Non-applicable, AMH: Anti-Müllerian hormone, CA125: Cancer antigen-125, ANGPTL4: Angiopoietin-like protein-4, PF: Peritoneal fluid

Serum and PF ANGPTL4 levels were significantly higher in women with stage IV endometriosis (n=23) than in those with stage III disease (n=17) (serum: 761.26±497.05 vs. 369.16±234.20 ng/mL, p=0.026; PF: 334.38±89.25 vs. 277.09±64.19 ng/mL, p=0.034). Multivariable linear regression analyses demonstrated that disease stage was independently associated with both serum and PF ANGPTL4 levels, whereas infertility, serum AMH, and serum CA125 were not independent predictors (Table 4).

Table 3. Diagnostic performance of serum CA125, serum ANGPTL4, and the combined CA125-ANGPTL4 model for the diagnosis of endometriosis

	AUC	SE	p-value	95% CI	Optimal cut-off value	Sensitivity (%)	Specificity (%)
CA125	0.888	0.037	<0.001*	0.815-0.962	16.30	85	72.5
Serum ANGPTL4	0.755	0.055	<0.001*	0.648-0.862	188.61	75	62.5
CA125 and serum ANGPTL4	0.931	0.026	<0.001*	0.879-0.982	-	-	-

*p-value <0.05 is considered as statistically significant. AUC: Area under curve, SE: Standard Error, CI: Confidence interval, CA125: Cancer antigen-125, ANGPTL4: Angiopoietin-like protein-4

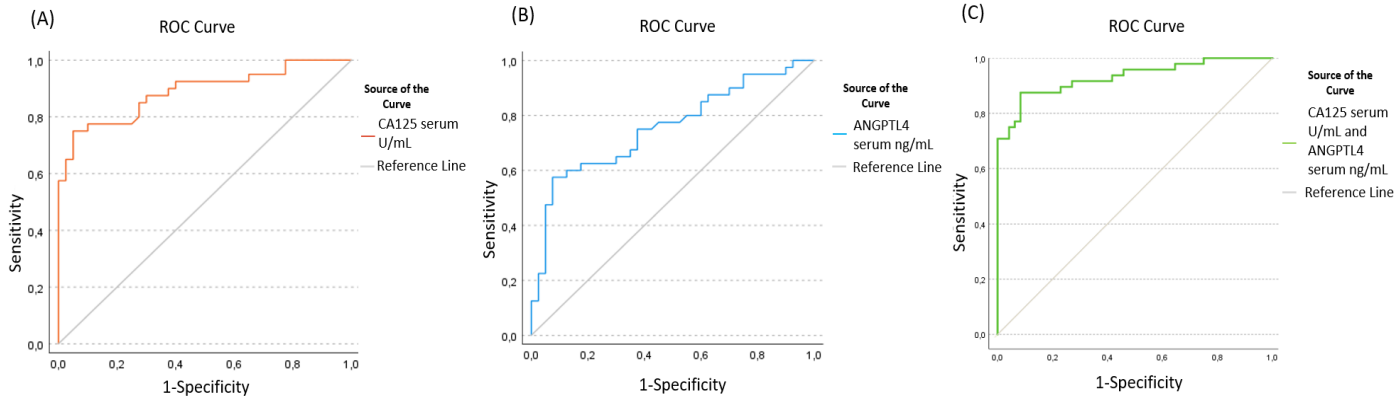

Figure 2. The ROC curves of serum CA125 (A), ANGPTL4 levels (B) and the combined serum CA125-ANGPTL4 (C) in endometriosis diasease

ROC: Receiver operating characteristic, CA125: Cancer antigen-125, ANGPTL4: Angiopoietin-like protein-4

Table 4. Multivariable regression analyses for serum and peritoneal fluid ANGPTL4 in the endometriosis group

Dependent variable	R^2-adjusted R^2	p-value	B (95% CI)	Independent predictors coefficients (standardized β)	p-value
Serum ANGPTL4, ng/mL	0.415-0.348	0.001*			
Disease stage (rASRM)			325.94 (88.07 to 563.81)	0.365	0.009*
Infertility			198.06 (-91.82 to 487.93)	0.219	0.174
Serum AMH, ng/mL			-54.89 (-172.69 to 62.92)	-0.151	0.351
Serum CA125, U/mL			0.77 (-0.17 to 1.71)	0.238	0.104
PF ANGPTL4, ng/mL	0.365-0.293	0.003*			
Disease stage (rASRM)			44.92 (1.40 to 91.24)	0.269	0.047*
Infertility			50.53 (-5.92 to 106.98)	0.299	0.078
Serum AMH, ng/mL			-4.73 (-27.67 to 18.21)	-0.070	0.678
Serum CA125, U/mL			0.16 (-0.03 to 0.34)	0.258	0.090

*p-value <0.05 is considered as statistically significant. Multivariable linear regression analyses were performed using the enter method. Standardized β coefficients and p-values are shown. Independent variables included disease stage (according to rASRM classification), infertility, serum AMH, and CA125. Variance inflation factors were <2 for all models, indicating no significant multicollinearity. ANGPTL4: Angiopoietin-like protein-4, rASRM: Revised American Society for Reproductive Medicine, AMH: Anti-Müllerian hormone, CA125: Cancer antigen-125, PF: Peritoneal fluid, CI: Confidence interval

Discussion

In the present study, women with endometriosis exhibited significantly higher serum ANGPTL4 levels compared with healthy controls. Serum ANGPTL4 levels were positively correlated with pelvic pain, dyspareunia, serum CA125 levels, and PFANGPTL4 concentrations, while showing a negative correlation with AMH levels. Furthermore, serum ANGPTL4 demonstrated a moderate ability to discriminate women with endometriosis from controls. Endometriosis is associated with a proinflammatory condition characterized by the presence of ectopic endometrial tissue (1,2). In the literature, ANGPTL4 was reported to contribute to vascular permeability, angiogenesis, and various immune pathways (12). The expression and secretion of ANGPTL4 have been closely linked to chronic inflammatory processes and macrophage-mediated immune responses so that ANGPTL4 is upregulated in response to inflammatory macrophages and modulates their phenotype in pathological conditions (6,13). Its expression has also been found to correlate with increases in pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6, suggesting that inflammatory signaling promotes ANGPTL4 expression, while anti-inflammatory pathways may oppose this effect (13). Previous studies have indicated that TNF-α and interferon-gamma play key roles in promoting the inflammatory response underlying the etiopathogenesis of endometriosis (14,15). However, to the best of our knowledge, the present study is the first to evaluate serum and/or PF ANGPTL4 levels in women with endometriosis. In our study, women with endometriosis demonstrated significantly elevated ANGPTL4 levels, and serum ANGPTL4 emerged as a potential discriminative biomarker for the disease. Although the discriminatory performance of serum ANGPTL4 alone was moderate (AUC =0.755), this finding suggests that ANGPTL4 may contribute to the clinical assessment of endometriosis rather than serving as a standalone diagnostic marker. Consistent with prior evidence, this novel observation appears biologically plausible and aligns with the inflammatory pathophysiology of the disease.

An additional finding of the present study was that both serum and PF ANGPTL4 levels were significantly higher in women with stage IV endometriosis than in those with stage III disease. Previous studies have shown that rASRM staging does not consistently correlate with symptom severity or clinical manifestations of endometriosis, and its ability to reflect disease burden remains limited (16). Similarly, CA125 has been shown to have limited value in accurately reflecting disease stage or severity (17). More broadly, biomarker studies in endometriosis have demonstrated significant heterogeneity in their association with disease severity, and no single biomarker has shown consistent performance across disease stages (18). In this context, multivariable modeling approaches are recommended to account for confounding clinical and hormonal factors when evaluating candidate biomarkers (18). Taken together, the present findings suggest that ANGPTL4 may be associated with both inflammatory activity and disease severity in endometriosis.

ANGPTL4 has been associated with gynecological conditions characterized by metabolic and inflammatory dysregulation, such as polycystic ovary syndrome, with increased expression in ovarian granulosa cells reported in affected women (19). In the current study, serum ANGPTL4 levels were also found to distinguish women with endometriosis from healthy controls. Cytokines present in the PF of women with endometriosis have been reported to directly enhance endometrial cell proliferation, invasion, and neovascularization, thereby facilitating lesion progression (20). Moreover, impaired clearance of endometrial cells by macrophages and natural killer cells may exacerbate abnormal cytokine production, sustaining peritoneal inflammation in endometriosis patients (18). The detection of ANGPTL4 in the PF of women with endometriosis may be clinically relevant, as it likely reflects local pelvic peritoneal inflammation. Furthermore, the significant correlation observed between serum and PF ANGPTL4 levels indicates that circulating ANGPTL4 may represent a non-invasive surrogate marker of pelvic inflammatory activity. Taken together, these findings suggest that serum ANGPTL4 may provide insight into both local and systemic inflammatory processes in endometriosis. The observed sensitivity and specificity further support its potential applicability as a biomarker in the clinical evaluation of the disease.

CA125, a recognized inflammatory marker, has been shown to increase in women with endometriosis (5). However, due to its limited specificity, recent studies have suggested that discovering new biomarkers will be important to enhance diagnostic accuracy in endometriosis (5). Consistent with previous studies, in the current study, serum CA125 levels were elevated in the endometriosis group. The alignment of our diagnostic sensitivity and specificity results with those reported in the literature (5) further supports the validity of our study population in representing endometriosis cases. Serum CA125, a widely used clinical marker in the evaluation of endometriosis, showed a significant correlation with both systemic and local ANGPTL4 levels. This association between ANGPTL4 and CA125 is particularly noteworthy, as it further reinforces the potential role of serum ANGPTL4 as a supportive biomarker in the clinical assessment of endometriosis.

After adjustment for relevant clinical and laboratory variables, serum ANGPTL4 was not independently associated with the presence of endometriosis. This finding suggests that the association between serum ANGPTL4 levels and endometriosis may be influenced by other clinical or biochemical factors.

An important finding of the present study is that the diagnostic performance of serum ANGPTL4 was not limited to its performance as an individual biomarker. When serum ANGPTL4 was incorporated into a multivariable logistic regression model with CA125, the resulting combined model demonstrated a higher discriminatory capacity than CA125 alone. Importantly, this improvement was statistically significant according to the DeLong test, supporting an incremental diagnostic contribution of serum ANGPTL4 beyond CA125. These findings suggest that serum ANGPTL4 may provide complementary diagnostic information to CA125 rather than simply representing an alternative biomarker. However, the clinical relevance of this combined diagnostic approach remains to be established.

Pain represents one of the most distressing symptoms in endometriosis. The complex interplay of elevated PF cytokines and chemokines has been implicated in driving both pelvic pain and dyspareunia (21). Notably, interleukin-8 and TNF-α are among key pro-inflammatory cytokines implicated in the pathophysiology of endometriosis. These mediators are associated with enhanced local inflammation, immune cell activation, and lesion development, which contribute to pain and disease progression. Pro-inflammatory signaling and cytokine dysregulation remain central features of endometriosis pathobiology (20,22). Women with endometriosis in this study reported higher VAS scores for pelvic pain and dyspareunia. ANGPTL4 levels were positively associated with the severity of pelvic pain and dyspareunia, and both serum and PF ANGPTL4 concentrations significantly correlated with pain severity. These observations constitute novel findings, highlighting a potential role of ANGPTL4 in the pathophysiology of endometriosis-associated pain. Considering the proinflammatory milieu in endometriosis at both local and systemic levels (2,20), the correlations between ANGPTL4, serum CA125 levels, and the severity of pelvic pain and dyspareunia are pathophysiologically consistent. These findings suggest that both systemic and local ANGPTL4 levels may have value in reflecting the clinical relevance of endometriosis-associated pain. Evaluation of ANGPTL4 in conjunction with pain-related cytokines and chemokines at both systemic and local levels may provide further clarification of this relationship in women with endometriosis. Furthermore, better understanding of ANGPTL4-related pathways may also contribute to improvement in therapeutic approaches targeting inflammation-associated pain.

Endometriosis has been linked to reduced ovarian reserve and impaired fertility, resulting from either the inflammatory milieu created by endometriotic foci or surgical treatment of lesions (23). AMH, produced by granulosa cells of small growing ovarian follicles, serves as a reliable biomarker for assessing the functional ovarian reserve and reflects the remaining follicular pool, making it a key early indicator of diminished ovarian function (24). Previous studies have reported decreased serum AMH levels in women with endometriosis, as well as an inverse correlation between serum CA125 and AMH levels (25). In line with previous evidence, women with endometriosis in this study had reduced serum AMH levels, which negatively correlated with serum CA125. Notably, given the reported inhibitory effects of ANGPTL4 on granulosa cell proliferation (26), our results demonstrated an inverse relationship between serum AMH and ANGPTL4 levels in both serum and PF, representing a novel finding of this study. Collectively, these findings support a potential association between inflammatory activity and ovarian reserve in endometriosis-related infertility.

Study limitations

The present study has several strengths and limitations that warrant consideration. A major strength is the definitive diagnosis of endometriosis confirmed by laparoscopy, together with the opportunity to assess local ANGPTL4 levels through PF sampling obtained during surgery. However, the invasive nature of PF collection limited the inclusion of healthy control samples. Given that AMH levels are known to decline with advancing age, higher BMI, and a history of prior ovarian surgery (23,27), the comparability of the study groups with respect to these variables further strengthens the validity of our findings.

The observed associations between ANGPTL4 levels, pain severity, CA125, and ovarian reserve markers suggest a potential role for ANGPTL4 in the clinical evaluation of women with endometriosis. In addition to reflecting inflammatory activity, its assessment alongside established clinical and laboratory parameters may provide complementary information regarding disease-related manifestations. Moreover, evaluating ANGPTL4 in conjunction with other inflammatory mediators may contribute to a better understanding of the biological mechanisms underlying endometriosis and its potential clinical applicability.

Conclusion

Inflammatory mechanisms play a central role in the pathogenesis of endometriosis, and accumulating evidence highlights the contribution of immune dysregulation to disease development. In line with this concept, the present study identifies ANGPTL4 as a potential mediator of the aberrant inflammatory response observed in endometriosis. These findings should be interpreted in the context of the study design and population characteristics. The significant correlation between serum and PF ANGPTL4 levels indicates that circulating ANGPTL4 may reflect local inflammatory activity. Taken together, the associations between ANGPTL4, clinical manifestations, and CA125 levels highlight its potential utility as a supportive clinical biomarker in the evaluation of women with endometriosis.

Ethics

Ethics Committee Approval: *The study was approved by Ankara Bilkent City Hospital Ethics Committee (approval no: TABED 1-25-1372, date: 04.06.2025) and National Institutes of Health Clinical Trial's Registry (#NCT07164196).*

Informed Consent: *Written informed consent was obtained from all participants.*

Footnotes

Author Contributions: *Surgical and Medical Practices: M.D.E.T., E.M.E.K., Concept: M.D.E.T., Design: M.D.E.T., E.M.E.K., Data Collection or Processing: M.D.E.T., Analysis or Interpretation: E.M.E.K., Literature Search: M.D.E.T., Writing: M.D.E.T., E.M.E.K.*

Conflict of Interest: *No conflict of interest is declared by the authors.*

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