Journal of
Controversies in Obstetrics & Gynecology and Pediatrics

Original Article

DOI: 10.51271/JCOGP-0069

Impact of dienogest therapy on CA125 levels, hormonal profile, and systemic inflammatory indices in endometriosis

Funda Bulut Arıkan*[1], Nevin Sağsöz[2]

[1]Department of Physiology, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkiye
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkiye

Cite this article as: Bulut Arıkan F, Sağsöz N. Impact of dienogest therapy on CA125 levels, hormonal profile, and systemic inflammatory indices in endometriosis. *J Controv Obstetr Gynecol Ped*. 2026;4(2):25-30. doi:10.51271/JCOGP-0069

***Corresponding Author**: Funda Bulut Arıkan, funbulut@kku.edu.tr

Received: 16.03.2026 ◆ **Accepted**: 18.04.2026 ◆ **Published**: 30.04.2026

ABSTRACT

Aims: The present study aims to evaluate the impact of dienogest therapy on CA125 levels, hormonal profile, and systemic inflammatory indices in patients with endometriosis, a chronic inflammatory disorder in which inflammation constitutes a fundamental component of the pathophysiology.

Methods: This retrospective, pre–post analytical study included 150 female with endometriosis who received dienogest. Demographic and laboratory data were obtained from electronic medical records. Systemic inflammatory indices including neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), neutrophil-to-monocyte ratio (NMR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), MPV-to-lymphocyte ratio (MPVLR), cancer antigen 125 (CA-125), Systemic Immune-inflammation Index (SII), Systemic Inflammation Response Index (SIRI), and pan-immune-inflammation value (PIV) were evaluated before and after treatment. Statistical analyses were performed using appropriate parametric and nonparametric tests, and correlation analyses were conducted.

Results: Following dienogest therapy, statistically significant reductions were observed in CA125 levels ($p=0.010$) and PLR ($p=0.028$), along with decreases in leukocyte, and PCT levels. FSH levels showed a significant increase ($p=0.001$), whereas LH, estradiol, progesterone, TSH, FT3, and FT4 levels remained unchanged ($p>0.05$ for all). Significant increases were also noted in hemoglobin, hematocrit, MCV, and MCH values after treatment ($p<0.05$). No statistically significant differences were detected in NLR, MLR, NMR, MPVLR, SII, SIRI, or PIV. Correlation analyses demonstrated a positive association between CA 125 and PLR, as well as inverse correlations between CA125 and hematocrit.

Conclusion: Dienogest therapy was associated with a reduction in CA125 levels and specific inflammatory markers, alongside improvements in certain hematological parameters in patients with endometriosis. These findings suggest a potential anti-inflammatory benefit, indicating that dienogest may be involved in the modulation of systemic inflammatory burden. Furthermore, the preservation of endocrine homeostasis may support its favorable safety profile as an effective therapeutic option in the management of endometriosis.

Keywords: Endometriosis, dienogest, CA125, systemic inflammation, hematological parameters

INTRODUCTION

Endometriosis is defined as the presence of endometrial glandular and stromal lesions localized outside the uterine cavity.[1,2] These lesions manifest phenotypically as peritoneal implants, superficial ovarian endometriosis, endometriomas, or deep infiltrating endometriosis. Although the precise etiology of endometriosis remains to be fully elucidated, several hypotheses have been proposed to explain the development of endometriotic lesions. The most widely accepted mechanisms include retrograde menstruation, Müllerian remnants that fail to undergo appropriate differentiation or migration during fetal development, and transdifferentiation of circulating blood cells into endometriotic tissue.[3,4] Inflammation plays a pivotal role in the pathophysiology of endometriosis. It has been demonstrated that inflammatory processes lead to the upregulation of key components of signaling pathways, such as mitogen-activated protein kinase (MAPK), which may constitute a potential therapeutic target in endometriosis.[1,5] In this context, dienogest, a synthetic progestin with well-established anti-inflammatory and anti-proliferative properties, is widely used in the management of endometriosis.[6]

Experimental animal models and in vitro cell culture studies have demonstrated that dienogest markedly suppresses the viability and proliferation of endometrial stromal cells stimulated by pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-32. This reduction was accompanied

by decreased expression of proliferating cell nuclear antigen and diminished phosphorylation of protein kinase B (AKT), indicating suppression of inflammatory signaling pathways.[7] Furthermore, another study demonstrated that dienogest downregulates the expression of inflammatory and neuroangiogenic mediators, such as cyclooxygenase-2 (COX-2), IL-6, IL-8, and vascular endothelial growth factor (VEGF), via progesterone receptor isoforms, thereby further supporting its anti-inflammatory effects.[8]

Systemic inflammatory indices have been extensively investigated in a broad spectrum of clinical disorders, including polycystic ovary syndrome (PCOS), hypertension, and diabetes mellitus.[9,10] However, there remains a notable paucity of studies evaluating the impact of dienogest on systemic inflammatory indices, including neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), neutrophil-to-monocyte ratio (NMR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), MPV-to-lymphocyte ratio (MPVLR), cancer antigen 125 (CA-125), Systemic Immune-inflammation Index (SII), Systemic Inflammation Response Index (SIRI), and pan-immune-inflammation value (PIV) in patients with endometriosis.

Accordingly, the present study aimed to comprehensively evaluate systemic inflammatory indices, including NLR, MLR, PLR, NMR, MPV, MPVLR, CA-125, SII, SIRI, and PIV, in patients with endometriosis/endometrioma, a disorder in which inflammation constitutes a central component of its underlying etiology.

METHODS

All necessary ethical approvals for this retrospective study were obtained from the Ethics Committee for Non-interventional Researches at Kırıkkale University (Date: 16.10.2024, Decision No: 2024.10.01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Protocol

This study was designed as a single-center, retrospective observational pre–post (paired) analytical study. Patients who were followed with a diagnosis of endometriosis at the Department of Obstetrics and Gynecology, Faculty of Medicine, Kırıkkale University, between January 2018 and September 2024. The study included patients treated with a daily 2 mg dose of dienogest for a mean duration of six months. Blood samples were collected on days 2-3 of the menstrual cycle to ensure standardized hormonal assessment. Patients diagnosed with endometriosis based on histopathological findings and those with ultrasonographic evidence of endometrioma were selected.

Demographic variables, including sex and age, along with laboratory parameters (e.g., complete blood count and biochemical profiles), were extracted from the hospital's electronic medical records. Based on these data, systemic inflammatory indices including NLR, MLR, NMR, PLR, MPV, MPVLR, SII, SIRI, and PIV were assessed before and after dienogest therapy in 150 female with endometriosis aged 18-50 years.

Inclusion Criteria

Participants were eligible for inclusion if they had a diagnosis of endometriosis or endometrioma confirmed by clinical and histopathological findings, had no history of chronic inflammatory disease, malignancy, or pregnancy, and had not used medications that could influence inflammatory status, including oral contraceptives, steroid hormones, insulin sensitizing agents, or anti inflammatory drugs, within the preceding six months.

Exclusion Criteria

Participants were excluded if they did not meet the diagnostic criteria for endometriosis or endometrioma based on clinical and histopathological findings, had a history of chronic inflammatory disease, malignancy, or pregnancy, had used medications that could affect inflammatory status, including oral contraceptives, steroid hormones, insulin sensitizing agents, or anti inflammatory drugs, within the preceding six months, or were younger than 18 years of age.

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics for Windows (version 27.0; IBM Corp., Armonk, NY, USA). The normality of the data distribution was assessed using appropriate tests. Normality analysis revealed that while PLCR (pre- and post-treatment), MPV (post-treatment), and LMR (pre- and post-treatment) exhibited a normal distribution ($p>0.05$), the remaining variables demonstrated a non-normal distribution ($p<0.05$). For comparisons of systemic inflammatory parameters before and after dienogest treatment, the paired Student's t-test was applied for normally distributed variables, whereas the Wilcoxon signed-rank test was used for non-normally distributed variables. Correlation analyses were conducted using two-tailed Pearson or Spearman correlation coefficients, as appropriate. Benjamini–Hochberg (FDR) correction was applied for multiple comparisons. Percentage change (Δ%) was calculated as [(after–before)/before]×100. The effect size (r) for the Wilcoxon signed-rank test was calculated using the formula $r=Z/\sqrt{N}$.

RESULTS

Variations in laboratory parameters before and after dienogest treatment are presented in **Table 1**. Regarding biochemical and hormonal assessments, a statistically significant reduction in serum CA125 levels was observed post treatment ($p=0.010$). Analysis of the hormonal profile revealed a significant elevation in FSH levels after the treatment period ($p=0.001$); however, other endocrine parameters, including LH, estradiol, prolactin, progesterone, TSH, FT3, and FT4, remained statistically stable ($p>0.05$ for all). In terms of hematological parameters, significant increases were noted in hemoglobin ($p=0.029$) and hematocrit ($p=0.002$) levels at the post-treatment evaluation. Correspondingly, red blood cell indices, specifically MCV ($p=0.012$) and MCH ($p=0.015$), demonstrated significant upward trends. Conversely, a significant decline was observed in leukocyte ($p=0.031$), and plateletcrit (PCT) ($p=0.009$) levels after therapy. Other markers, such as RDW, PDW, MPV, and P-LCR, exhibited no significant alterations ($p>0.05$). Notably, after applying the Benjamini-Hochberg False Discovery Rate (FDR) correction for multiple comparisons, platelet counts (PLT) failed to maintain statistical significance ($q>0.05$), despite an initial marginal p-value of 0.046. Analysis of inflammatory indices revealed that PLR levels significantly declined after the treatment period ($p=0.028$), However, no statistically significant differences were observed in NLR, LMR, NMR, MPVLR, SII, SIRI, or PIV values ($p>0.05$ for all).

Table 1. Comparison of laboratory parameters before and after treatment

Parameters	Before (median, IQR)	After (median, IQR)	p value
Ovarian markers			
CA125 (U/ml)	33.50 (22.00-47.50)	21.00 (15.00-36.00)	0.010*
Hormonal profile			
FSH (mIU/ml)	6.10 (4.50-8.00)	6.55 (4.90-11.10)	0.001*
LH (mIU/ml)	8.00 (5.00-12.00)	8.50 (5.60-14.80)	0.125
Estradiol (pg/ml)	90.00 (50.00-165.00)	90.00 (58.00-143.00)	0.791
Prolactin (ng/ml)	16.00 (11.00-21.00)	16.00 (11.00-21.00)	0.442
Progesterone (ng/ml)	1.10 (0.40-4.00)	1.20 (0.50-5.00)	0.156
Thyroid function			
TSH (mIU/L)	1.70 (1.10-2.40)	1.60 (1.10-2.40)	0.616
FT3 (pg/ml)	3.00 (2.80-3.30)	3.00 (2.80-3.40)	0.643
FT4 (ng/dl)	1.20 (1.10-1.30)	1.20 (1.10-1.30)	0.878
Hematological parameters			
Hemoglobin (g/dl)	12.60 (11.50-13.60)	12.90 (11.90-14.00)	0.029*
Hematocrit (%)	38.00 (35.70-41.00)	39.50 (36.80-41.90)	0.002*
Leukocyte ($x10^3/\mu L$)	7.40 (6.10-9.30)	7.10 (5.90-8.30)	0.031*
MCV (fL)	86.00 (80.00-89.00)	86.00 (82.00-90.00)	0.012*
MCH (pg)	28.50 (26.30-30.00)	28.80 (26.60-30.40)	0.015*
Inflammatory indices			
PLR	134.00 (104.00-172.00)	125.00 (104.00-152.00)	0.028*
SII	602.00 (413.00-846.00)	572.00 (421.00-817.00)	0.111
SIRI	0.88 (0.50-1.30)	0.90 (0.50-1.40)	0.646
PIV	212.00 (126.00-393.00)	224.00 (133.00-412.00)	0.471

CA125: Cancer antigen 125, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, TSH: Thyroid stimulating hormone, RDW: Red cell distribution width, PDW: Platelet distribution width, MPV: Mean platelet volume, PCT: Plateletcrit, PLCR: Platelet large cell ratio, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte, ratio, PLR: Platelet-to-lymphocyte ratio, NMR: Neutrophil-to-monocyte ratio, MPVLR: MPV-to-lymphocyte ratio, SII: Systemic Immune-inflammation Index, SIRI: Systemic Inflammation Response Index, PIV: Pan-immune-inflammation value. After applying the Benjamini-Hochberg (FDR) correction for multiple comparisons, the difference in platelet (PLT) levels did not reach statistical significance (adjusted p=0.052)

Percentage change and effect size of laboratory parameters following dienogest treatment are presented in **Table 2**. After treatment, CA125 levels decreased by 15.1%, whereas FSH levels increased markedly by 31.0%. Hemoglobin and hematocrit increased by 2.6% and 2.5%, respectively, accompanied by modest increases in MCV (+1.0%) and MCH (+1.2%). A downward trend in systemic inflammation was also observed, reflected by a 7.5% reduction in PLR and a 5.1% decrease in leukocyte counts (**Table 2**). Correlation analysis between systemic inflammatory markers and hematological parameters is presented in **Table 3**.

Table 2. Percentage change and effect size of laboratory parameters following dienogest treatment

Parameter	Before	After	Δ% change	Effect size (r)
CA125	42.49	36.06	−15.1% ↓	0.21
FSH	8.75	11.46	+31.0% ↑	0.27
Hematocrit	38.26	39.23	+2.5% ↑	0.21
Hemoglobin	12.56	12.89	+2.6% ↑	0.21
Leukocyte	7.78	7.38	−5.1% ↓	0.18
Platelet	287.81	282.84	−1.7% ↓	0.16
PCT	0.30	0.28	−6.7% ↓	0.18
MCV	84.72	85.56	+1.0% ↑	0.21
MCH	27.93	28.26	+1.2% ↑	0.20
PLR	145.63	134.74	−7.5% ↓	0.18

CA125: Cancer antigen 125, FSH: Follicle stimulating hormone, PCT: Plateletcrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, PLR: Platelet-to-lymphocyte ratio

DISCUSSION

In the present study, dienogest therapy, a selective progestin, was associated with reductions in CA125 levels, a well-recognized marker of endometriosis activity, along with decreases in systemic inflammatory parameters including PLR and PCT. Concurrently, a significant increase in FSH

Table 3. Correlation analysis between systemic inflammatory markers and hematological parameters

	CA125	FSH	Hb	HCT	WBC	PLT	PCT	MCV	MCH	PLR
CA125	1.00	-0.342 (0.042)*	-0.014 (0.891)	-0.277 (0.006)**	0.042 (0.680)	0.041 (0.683)	0.087 (0.487)	-0.123 (0.228)	-0.228 (0.028)*	0.249 (0.013)*
FSH	-0.342 (0.042)*	1.00	-0.059 (0.581)	-0.093 (0.382)	-0.066 (0.538)	-0.010 (0.930)	-0.135 (0.279)	-0.116 (0.276)	-0.093 (0.382)	0.060 (0.582)
HB	-0.014 (0.891)	-0.059 (0.581)	1.00	0.933 (<0.001)**	-0.071 (0.404)	-0.116 (0.173)	-0.155 (0.069)	0.308 (<0.001)**	0.499 (<0.001)**	-0.144 (0.090)
HCT	-0.277 (0.006)**	-0.093 (0.382)	0.933 (<0.001)**	1.00	-0.054 (0.529)	-0.096 (0.258)	-0.136 (0.108)	0.306 (<0.001)**	0.518 (<0.001)**	-0.119 (0.161)
WBC	0.042 (0.680)	-0.066 (0.538)	-0.071 (0.404)	-0.054 (0.529)	1.00	0.220 (0.009)**	0.207 (0.014)*	-0.083 (0.325)	-0.200 (0.018)*	-0.072 (0.399)
PLT	0.041 (0.683)	-0.010 (0.930)	-0.116 (0.173)	-0.096 (0.258)	0.220 (0.009)**	1.00	0.877 (<0.001)**	-0.073 (0.390)	-0.156 (0.066)	0.488 (<0.001)**
PCT	0.087 (0.487)	-0.135 (0.279)	-0.155 (0.069)	-0.136 (0.108)	0.207 (0.014)*	0.877 (<0.001)**	1.00	-0.019 (0.823)	-0.114 (0.181)	0.444 (<0.001)**
MCV	-0.123 (0.228)	-0.116 (0.276)	0.308 (<0.001)**	0.306 (<0.001)**	-0.083 (0.325)	-0.073 (0.390)	-0.019 (0.823)	1.00	0.824 (<0.001)**	-0.005 (0.955)
MCH	-0.228 (0.028)*	-0.093 (0.382)	0.499 (<0.001)**	0.518 (<0.001)**	-0.200 (0.018)*	-0.156 (0.066)	-0.114 (0.181)	0.824 (<0.001)**	1.00	-0.075 (0.380)
PLR	0.249 (0.013)*	0.060 (0.582)	-0.144 (0.090)	-0.119 (0.161)	-0.072 (0.399)	0.488 (<0.001)**	0.444 (<0.001)**	-0.005 (0.955)	-0.075 (0.380)	1.00

*Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed). FSH: Follicle-stimulating hormone, PCT: Procalcitonin, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, PLR: Platelet-to-lymphocyte ratio. Following the Benjamini-Hochberg (FDR) correction for multiple comparisons, certain correlations that initially appeared significant did not maintain statistical significance (q>0.05), including CA125 and FSH (p=0.042→q=0.118), CA125 and MCH (p=0.028→q=0.084), and Leukocyte and MCH (p=0.018→q=0.057).

levels was observed, which may suggest that the pituitary axis was not entirely suppressed. Furthermore, the noted improvements in hematological parameters could potentially be attributed to a reduction in menstrual blood loss associated with the therapy. Endometriosis is widely recognized as a systemic inflammatory condition in the literature. The present findings may suggest a suppressive effect of dienogest on this inflammatory milieu. Significant reductions in leukocyte was observed, accompanied by a notable decrease in PLR, a well-established marker of systemic inflammation. Furthermore, the observed reduction in PCT levels, a marker of platelet activation, provides additional evidence for the attenuation of systemic inflammatory activity.

In line with our findings, a case control study demonstrated that systemic inflammatory markers, including NLR and PLR, were significantly elevated in patients with endometriosis compared with healthy controls. However, in contrast to our results, SII, SIRI, and PIV indices were also reported to be elevated in that study.[11] Moreover, a large-scale study involving over 10,000 patients identified a positive correlation between NLR and PLR, further supporting their utility as biomarkers of systemic inflammation in ovarian endometriosis.[12] Similarly, elevated PCT levels have been reported in patients with endometriosis.[13]

To the best of our knowledge, this is the first study to evaluate systemic inflammatory indices before and after dienogest therapy, marking a novel contribution to the existing literature. In this context, a study investigating RNA expression profiles in endometriotic tissues from patients receiving or not receiving preoperative dienogest demonstrated that dienogest modulates leukocyte activation and inflammatory signaling pathways at the molecular level.[14] The reductions in leukocyte count and PLR observed following treatment in the present study may therefore be interpreted as clinical reflections of these molecular regulatory effects. Notably, the 7.5% reduction in PLR following dienogest therapy further supports the notion that medical treatment effectively modulates the underlying inflammatory process and reduces systemic inflammatory burden.

In the present study, the 15.1% reduction in CA125 levels, a well-established biomarker associated with both epithelial ovarian cancer and endometriosis,[15] is consistent with the suppressive effects of dienogest on endometriotic lesions reported in the literature.[16] This decrease is clinically relevant, as it may reflect suppression of inflammatory activity and cellular proliferation within ectopic endometrial tissue or indicate regression of the underlying pathological process.

Another notable finding was the 31.0% increase in FSH levels. Previous evidence suggests that dienogest exerts only a moderate suppressive effect on gonadotropins. In one study, this modulatory effect enabled effective LH suppression without complete inactivation of the pituitary axis.[17] The increase in FSH observed in our study may therefore be interpreted as a dynamic response of the pituitary axis to partial suppression or as a rebound effect[18] However, no statistically significant differences were observed in LH, estradiol, or progesterone levels ($p>0.05$). While several parameters reached statistical significance ($p<0.05$), the observed effect sizes were generally small ($r<0.3$), suggesting that the immediate clinical magnitude of these changes may be limited. However, in the context of a chronic inflammatory disease like endometriosis, these alterations such as the 2.6% increase in hemoglobin and the 15.1% reduction in CA125 should be interpreted as positive biological trends rather than transformative clinical shifts.

These findings indicate that dienogest does not fully suppress the hypothalamic–pituitary–gonadal axis but rather maintains a therapeutic window at the target tissue level. By maintaining estrogen levels within a specific therapeutic window, dienogest appears to exert a protective effect on bone mineral density.[19] Supporting this observation, a case study reported that progestin therapy combined with low-dose estrogen in symptomatic patients unresponsive to conventional progestin and GnRH analog treatments resulted in complete resolution of clinical symptoms and an increase in bone mineral density over a two-year follow-up period.[20]

One of the most striking findings of the present study is the improvement observed in the hematological profile of the patients. The significant increases in hemoglobin, hematocrit, MCV, and MCH following treatment suggest a clinical consequence potentially related to dienogest-induced amenorrhea. In endometriosis, which is characterized by chronic pelvic pain and menstrual bleeding,[3] the prevention of blood loss reduces the risk of iron deficiency anemia, contributes to the preservation of iron stores, and improves overall patient condition. These findings may suggest that the therapeutic impact of dienogest could extend beyond the suppression of endometriotic lesions, potentially contributing to improvements in the patients' overall anemia profile. The observed increases in hematological parameters, particularly hemoglobin and hematocrit, appear to indicate that the intervention is unlikely to induce significant adverse effects such as bone marrow suppression; instead, it might support a more favorable general health status in this patient population. In contrast, no statistically significant differences were observed in more complex inflammatory indices, including NLR, SII, and SIRI. Consistent with previous studies, these findings suggest that the anti inflammatory effects of dienogest are primarily mediated through modulation of platelet and leukocyte homeostasis,[11,14] without markedly altering the neutrophil lymphocyte balance.

In the present study, the positive correlation identified between CA125 levels and the platelet to lymphocyte ratio PLR supports the hypothesis that endometriosis is not solely a localized pelvic disorder but also represents a systemic inflammatory condition.[1] In line with this finding, previous studies have reported that both PLR and CA125 levels are positively correlated with the severity of pelvic adhesions and that the combined use of these two parameters demonstrates high diagnostic specificity.[21] This positive association between CA125 and PLR suggests that the inflammatory burden of the disease can be monitored concurrently through both biochemical and hematological parameters.

The inverse relationship between CA125 and hematocrit observed in our study is further supported by recent longitudinal data demonstrating that women with endometriosis carry a significantly higher risk of iron deficiency, while Kawamata et al.[23] highlighted that anemia-related biomarkers are closely

linked to the clinical characteristics of the disease. In this context, the statistically significant increase in hemoglobin and hematocrit following dienogest treatment, likely mediated by a reduction in menstrual blood loss and mitigation of chronic inflammation, represents a clinically meaningful improvement in the patients' hematological health. This finding aligns with the therapeutic goals outlined in recent literature.[22,23] The significant positive correlation observed between CA125 and PLR is consistent with the findings of Sabarudin et al.,[24] reinforcing the biological plausibility that CA125 levels parallel systemic inflammatory indices in gynecological pathologies and that dienogest treatment effectively modulates both localized disease activity and this systemic inflammatory environment. In the present study, hematological parameters exhibited internal consistency. The positive correlation observed between leukocyte count and platelet and PCT levels further supports the interaction among hematological cell lineages in the context of subclinical inflammation reported in patients with endometriosis.[11]

Limitations

The primary limitation of this study is its retrospective nature, which prevents the establishment of a direct causal relationship. Furthermore, while the current sample size provides significant data, further large-scale, multicenter studies are warranted to enhance the generalizability of the findings.

CONCLUSION

Dienogest therapy was associated with a reduction in CA125 levels and certain systemic inflammatory markers, alongside improvements in hematological parameters. These findings suggest that dienogest may modulate specific pathways of systemic inflammation without achieving complete suppression of the hypothalamic–pituitary–gonadal axis.

ETHICAL DECLARATIONS

Ethics Committee Approval

All necessary ethical approvals for this retrospective study were obtained from the Ethics Committee for Non-interventional Researches at Kırıkkale University (Date: 16.10.2024, Decision No: 2024.10.01).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: FBA, NS; Design: FBA, NS; Control: FBA, NS; Data Collection and/or Processing: FBA; Analysis and/or Interpretation: FBA, NS; Literature Review: FBA, NS; Writing the Article: FBA, NS; Critical Review: FBA, NS.

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Funda Bulut Arıkan
Assoc. Prof. Dr. Funda Bulut Arıkan is a faculty member in the Department of Physiology at Kırıkkale University Faculty of Medicine. She completed her specialization in Physiology at Firat University. Her research interests primarily focus on endocrine physiology and neurophysiology, as well as systemic inflammation, oxidative stress, and hematological and biochemical biomarkers, with particular emphasis on their roles in disease pathophysiology. Dr. Funda Bulut Arıkan has published numerous articles in national and international peer reviewed journals and has contributed significantly to the scientific literature in her field. She is actively engaged in academic research, mentoring, and interdisciplinary collaborations.