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Letter to the Editor

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Comments on the interpretation of the effects of dienogest therapy on CA125 and systemic inflammatory indices in endometriosis

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Dear Editor,

We read with great interest the article by Bulut Arıkan and Sağsöz[1] entitled "Impact of dienogest therapy on CA125 levels, hormonal profile, and systemic inflammatory indices in endometriosis." The authors' effort to evaluate the effects of dienogest treatment on CA125, hormonal profile, and systemic inflammatory indices in women with endometriosis represents a valuable contribution to the literature.[1,2] However, we believe that certain aspects of the study design and interpretation of the findings warrant a more cautious discussion.[1,3]

First, the study has a single-center, retrospective, uncontrolled pre-post design.[1] In such retrospective designs, the use of existing records and the absence of randomization inherently limit control over exposure and concomitant factors and may introduce selection bias and residual confounding.[3] Consequently, the post-treatment changes observed in laboratory parameters can only be attributed to dienogest with considerable caution, as time-related trends, co interventions, and unmeasured confounders cannot be excluded.[3] Although statistically significant p values are reported, the effect sizes appear generally small; for instance, the authors describe approximately a 15.1% reduction in CA125 and a 7.5% reduction in PLR, with modest increases in hemoglobin and hematocrit.[1] These findings support favorable biological trends but do not necessarily imply robust clinical impact, which should be explicitly discussed.[3]

Second, the authors conclude that dienogest modulates systemic inflammatory burden and exerts an anti inflammatory effect.[1] However, in the presented results, statistically significant improvement in inflammatory indices is essentially limited to PLR, whereas no significant differences are observed in NLR, SII, SIRI, or PIV.[1] Considering that systemic inflammation is usually inferred from consistent changes across multiple markers,[4] this pattern suggests that the anti inflammatory effect on systemic inflammation may be selective or limited rather than global. Thus, statements implying a marked reduction in systemic inflammatory load may be stronger than what the data support, and a more conservative wording, such as "improvement in selected hematological and inflammatory markers," could be more appropriate.[1,4]

Third, the increase in hemoglobin and hematocrit is plausibly attributed by the authors to reduced menstrual blood loss and mitigation of chronic inflammation.[1] This hypothesis is biologically reasonable, particularly in light of data showing an increased risk of iron deficiency in women with endometriosis.[5] Nevertheless, the study does not provide clinical outcomes such as bleeding pattern, pain scores, quality of life, or lesion size.[1] Without these measures, linking hematological improvement directly to amenorrhea or reduction in heavy menstrual bleeding remains speculative, and the clinical significance of these changes cannot be fully established.[3-5] Similarly, the observed increase in FSH is interpreted as preservation of endocrine homeostasis and incomplete suppression of the hypothalamic-pituitary-gonadal axis; yet no clinical safety parameters (e.g., menopausal symptoms, bone mineral density, long term adverse events) are presented to substantiate this interpretation.[1]

In summary, this study offers useful preliminary data on the potential effects of dienogest on laboratory markers in patients with endometriosis.[1] However, the retrospective, uncontrolled design, small effect sizes, and absence of detailed clinical endpoints indicate that the reported anti inflammatory activity and hematological improvement should be interpreted with caution.[2-5] Prospective, controlled studies incorporating robust clinical outcomes are needed to better define the true clinical impact of dienogest on systemic inflammation and overall health status in this patient population.[3-5] We appreciate the authors' contribution to this important field and look forward to future research that will further clarify these issues.[1]

ETHICAL DECLARATIONS

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Letter to the Editor

Author reply " Comments on the interpretation of the effects of dienogest therapy on CA125 and systemic inflammatory indices in endometriosis"

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Dear Editor,

We would like to express our sincere appreciation for the insightful comments and constructive critiques provided by the authors regarding our article entitled "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), published in a recent issue of your journal. This scholarly exchange is highly valuable, as it offers an opportunity to further clarify and contextualize the contribution of our work within the existing literature. Our responses to the raised points are presented below in a structured manner:

- **Regarding study design, causal inference, and scientific language:** The authors correctly emphasize that the retrospective, single-center, and uncontrolled pre-post design of our study inherently limits causal inference and external validity. We fully agree with this methodological reality. Indeed, in the Limitations section of our published manuscript, we proactively addressed this issue and explicitly stated the following: "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."

In addition, we concur with the authors' interpretation regarding the inferential limitations associated with causal attribution and clinical generalizability. Accordingly, a careful review of the abstract and discussion sections demonstrates that all interpretations were deliberately framed within a cautious scientific paradigm. Assertions of causality or overgeneralization were systematically avoided, and instead, standard academic hedging terminology-such as "associated with," "may exert," "suggest a potential benefit," and "may be involved"-was consistently employed in accordance with established scientific writing conventions. The study is based on a relatively robust cohort of 150 patients reflecting real-world clinical data; however, the findings were not presented as definitive or transformative evidence, and the necessity for prospective, multicenter validation studies was explicitly emphasized.

- **Regarding differential changes in systemic inflammatory indices:** The authors highlight that, despite a statistically significant reduction in platelet/lymphocyte ratio (PLR) (p=0.028), no significant changes were observed in neutrophil/lymphocyte ratio (NLR), Systemic Immune-inflammation Index (SII), or Systemic Inflammation Response Index (SIRI), and suggest that this finding may be inconsistent with the hypothesis of a broad systemic anti-inflammatory effect. As explicitly stated in the abstract, "Dienogest therapy was associated with a reduction in CA125 levels and specific inflammatory markers, alongside improvements in certain hematological parameters in patients with endometriosis," where the deliberate use of the qualifiers "specific" and "certain" precludes any claim of generalized systemic anti-inflammatory effects.

Endometriosis is a complex and highly heterogeneous inflammatory disorder, characterized by differential activation of immunological and hematological pathways. Consequently, inflammatory modulation does not necessarily manifest uniformly across all systemic biomarkers. As elaborated in the discussion section, platelets play a central and mechanistically specific role in endometriotic lesion progression, including angiogenesis, stromal proliferation, and tissue remodeling. In this context, the observed statistically significant reductions in leukocyte count (p=0.031), PLR (p=0.028), and plateletcrit (PCT) (p=0.009) are indicative of targeted attenuation of discrete subclinical inflammatory pathways.

Consistent with this interpretation, emerging evidence in the literature suggests that dienogest may exert selective immunomodulatory effects, particularly on platelet and leukocyte homeostasis, rather than inducing broad alterations in neutrophil-lymphocyte dynamics. Notably, recent studies by Kurt et al.[11] and Chung et al.[14] have demonstrated gene-level and cellular regulatory effects of dienogest on hematological homeostasis. Accordingly, the absence of significant changes in NLR or SII does not diminish the relevance of the observed reductions in PLR and PCT; rather, it underscores the pathway-specific nature of immune modulation under progestin therapy. Furthermore, a statistically significant positive correlation between CA125 and PLR was identified, suggesting that CA125 levels in endometriosis may reflect systemic inflammatory burden, in accordance with previous literature.

- **Regarding hematological outcomes, endocrine stability, and clinical interpretation:** The authors propose that, in the absence of detailed clinical outcome measures, the proposed mechanisms underlying hematological improvement and endocrine stability remain speculative. We respectfully disagree with this interpretation. In contemporary clinical physiology and reproductive medicine, validated biochemical and hematological indices are widely accepted as objective and clinically meaningful endpoints, particularly in mechanistic and translational research contexts.

In this study, the effects of dienogest therapy were evaluated using a comprehensive panel of objectively measurable clinical parameters, including CA125 levels, hormonal profile, thyroid function tests, hematological indices, and systemic inflammatory markers, thereby providing a multidimensional and integrated assessment of treatment-related physiological effects.

- **Endocrine stability:** The concept of "endocrine stability" as used in this study is not speculative, but rather directly derived from the empirical findings presented in **Table 1**. Although the retrospective design limited access to certain standardized post-treatment imaging datasets, the endocrine profile demonstrated consistent homeostatic preservation. Specifically, serum concentrations of LH, estradiol, prolactin, progesterone, TSH, FT3, and FT4 remained statistically unchanged following treatment (all $p>0.05$). While a statistically significant variation in FSH levels was observed, this change remained entirely within established physiological reference ranges. Preservation of hypothalamic-pituitary-thyroid and hypothalamic-pituitary-gonadal axis integrity within normative limits is widely recognized in the literature as a key indicator of endocrine stability.

- **Hematological outcomes:** The statistically significant increases in hemoglobin ($p=0.029$), hematocrit ($p=0.002$), mean corpuscular volume (MCV) ($p=0.012$), and mean corpuscular hemoglobin (MCH) ($p=0.015$) represent robust and clinically meaningful hematological improvements. In the context of endometriosis, a chronic condition frequently associated with dysmenorrhea and heavy menstrual bleeding, the observed hematological improvements are physiologically consistent with reduced menstrual blood loss secondary to dienogest-induced ovulatory suppression and amenorrhea. This represents a well-established pathophysiological mechanism rather than a speculative inference.

In conclusion, we sincerely thank the authors for their careful and critical appraisal of our work. Their comments have contributed to a more nuanced interpretation of our findings. We maintain that our study provides objective and clinically relevant evidence regarding the hematological and inflammatory effects of dienogest and constitutes a meaningful contribution to the literature, while also underscoring the need for future prospective, multicenter investigations.

Respectfully,