Research Article

Evaluation of Estradiol and Pro-Inflammatory Marker Level with VAS Score After Progestin Therapy in Endometriosis Patients

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Abstract

Objectives: To compare estradiol levels and proinflammatory biomarkers (IL-6, IL-1β, and COX-2) in endometriosis patients with pain and without pain after progestin therapy.

Methods: This observational cross-sectional study involved 47 endometriosis patients undergoing three months of progestin therapy at RSUPN Cipto Mangunkusumo from March to June 2024. Serum levels of COX-2, IL-6, IL-1β, and estradiol will be measured using ELISA and Microplate Enzyme Immunoassay, with pain status assessed to determine associations between biomarkers and pain presence.

Results: A significant difference in COX-2 levels between patients with pain and those without, with higher levels in the pain group [1.845 (1.24-10.26) vs 1.55 (0.32-3.07), p = 0.004]. A significant positive correlation was found between IL-1β and IL-6 (r = 0.471, p = 0.001). COX-2 levels also exhibited a weak but statistically significant positive correlation with VAS scores (r = 0.360, p = 0.013).

Conclusion: There is a difference in inflammatory markers IL-6, IL-β and COX-2 in endometriosis patients with progestin therapy who experience pain and painlessness.

Keywords: endometriosis, estradiol, proinflammation, progestin therapy.

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INTRODUCTION

Endometriosis is a condition characterized by the growth of endometrial-like tissue outside the uterus. Endometriosis is estrogen-dependent, so clinical symptoms typically manifest when a woman reaches reproductive age.[1, 2] The condition affects approximately 10% of young women, representing around 200 million women of reproductive age. Its prevalence increases to up to 50% among patients with chronic pelvic pain, infertility, or both.[3]

One evolving theory regarding the pathophysiology of endometriosis is the Tissue Injury and Repair (TIAR) concept. This theory is based on the idea that the disease develops spontaneously due to repeated microtrauma from chronic uterine peristaltic activity affecting the endometrium-myometrium boundary.[4] This condition heightens the inflammatory response by increasing COX-2 levels, elevating prostaglandin E2 (PGE2) levels. Elevated PGE2 activates STAR (steroidogenic acute regulatory protein) and P450 aromatase.[4]

In endometriosis patients, there is an increased expression of COX-2 and PGE2, which induces inflammation. The elevated levels of these compounds further increase estradiol levels, exacerbating pro-inflammatory factors.[5] The increased pro-inflammatory factors are the secretion of IL-6 and IL-1β.[6] The increase in pro-inflammatory factors enhances the recruitment of peripheral nerve fibres associated with pain sensitization, specifically C-fibers. The elevated

density of these nerve fibers contributes to the development of pain.[6,7]

Based on this pathophysiology, estrogen plays a crucial role in the development of endometriosis and is closely associated with the production of pro-inflammatory cytokines, which contribute to pain.1 Progestin therapy is one of the hormonal treatments that can suppress estrogen production, both from the ovaries and within endometriotic lesions, thereby reducing pain stimulation caused by endometriosis lesions. In the hypothalamic-pituitary-ovarian axis, progestin therapy can inhibit the release of GnRH, and the levels of FSH and LH. The decrease in gonadotropin levels subsequently leads to reduced ovarian steroid hormone levels, which can cause amenorrhea and prevent endometrial reflux.[8]

Progestin has antimitotic effects on endometrial cells, inhibiting aromatase enzyme activity, COX-2 expression, and PGE2 production in endometrial cell cultures. This action helps to reduce or suppress inflammatory reactions in the pelvic cavity and alleviate pain.[9, 10] In addition to inducing apoptosis and atrophy in endometriotic implants, progestin also plays a role in reducing angiogenic factors such as VEGF, which can decrease the survival rate of endometriosis lesions.[10,11] Compared to GnRH agonist therapy, progestin provides similar effects with higher tolerability and without the side effects commonly associated with GnRH agonists, such as vasomotor symptoms, loss of bone mineral density, vaginal dryness, and decreased libido.[12-14]

Despite this, progestin therapy does not completely eliminate pain complaints in patients with endometriosis. There are phenotypic subgroups of patients who continue to experience pain despite receiving therapy. The persistence of pain in these patients may be attributed to elevated levels of pro-inflammatory compounds and serum estrogen. Therefore, this study aims to evaluate the levels of pro-inflammatory markers IL-6, IL-1β, and COX-2, as well as serum estradiol, in endometriosis patients with and without pain undergoing progestin therapy.

METHODS

This observational cross-sectional study aims to compare serum levels of COX-2, IL-6, IL-1β, and estradiol in patients with endometriosis who are undergoing long-term (3-month) progestin therapy. The research will differentiate between those experiencing pain and those who are not. Conducted at RSUPN Cipto Mangunkusumo in Jakarta from March to June 2024, or until the sample size is achieved, the study will adhere to the guidelines set by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia - RSUPN Cipto Mangunkusumo. Approval has been granted under the number KET-1181/UN2.F1/ETIK/PPM.00.02.2024, and written informed consent will be obtained from all participants regarding the procedures involved.

The target population for this study consists of endometriosis patients receiving long-term (three months) progestin therapy at RSUPN Cipto Mangunkusumo from March to June 2024, who meet the inclusion and exclusion criteria. Inclusion criteria are patients with endometriosis diagnosed via ultrasound or laparoscopy, receiving three months of progestin therapy, exclusively using progestin without other modalities (such as GnRH agonists or aromatase inhibitors), and aged 18–45 years. Exclusion criteria include patients with autoimmune diseases (lupus, Sjögren's syndrome, rheumatoid arthritis), PCOS, a history of hypertension, diabetes mellitus, or dyslipidemia, those undergoing treatment for other infections, and patients with pelvic inflammatory disease. Consecutive sampling will be used to obtain 47 subjects who meet the inclusion and exclusion criteria.

The study procedure involves identifying and selecting endometriosis patients who have received long-term progestin therapy from March to June 2024 at the RSCM outpatient clinic, based on inclusion and exclusion criteria. Patients who meet the criteria will be evaluated through medical records concerning endometriosis phenotype, surgical history, progestin use, other treatments, pain complaints, abnormal uterine bleeding, and the volume of blood loss. Blood samples will be collected at the clinic, analyzed at the IMERI laboratory, and the results will be processed statistically.

The levels of pro-inflammatory markers IL-1β, IL-6, and COX-2 will be measured using the sandwich ELISA method. For the analysis of IL-1β and IL-6, samples will be diluted and analyzed through a procedure involving incubation, washing, addition of antibodies and substrates, followed by reading the results using a microplate reader at 450 nm. Serum estrogen levels will be assessed using Microplate Enzyme Immunoassay. Serum samples, calibrators, and controls will be tested in duplicate.

The procedure includes the addition of reagents, incubation, washing, addition of substrate solution, and reading the results at 450 nm. Data analysis will be conducted using SPSS version 23.0. The independent variables in this study are serum levels of COX-2, IL-6, IL-1β, and estradiol. The dependent variable is the presence or absence of pain. Data will be presented as mean ± standard deviation (SD) for normally distributed data or median (interquartile range, IQR) for non-normally distributed data. Statistical tests used to evaluate the effectiveness of the treatment include the independent T-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data.

RESULTS

Table 1. Basic Characteristics of Patients

Variables	Total (n = 47)
Age: Median (min-max), years	40(27-45)
Body Weight: Mean ± SD, kg	62.4±11.8
Height: Mean ± SD, cm	155.9±5.6
Body Mass Index (BMI): Mean ± SD, kg/m²	25.6±4.6
Endometriosis Phenotype	
Endometrioma	
Yes	26 (55.3)
No	21 (44.7)
Endometrioma Location	
Unilateral	15 (57.7)
Bilateral	11 (42.3)
Adenomyosis	
Yes	42 (89.4)
No	5 (10.6)
Deep Endometriosis	
Yes	1 (2.1)
No	46 (97.8)
Surgical Intervention	
Yes	22 (46.8)
No	25 (53.2)
Progestin Used	
Type of Medication	
Oral	44 (93.6)
Implant	3 (6.4)
Medication Type	
Lynestrenol	11 (23.4)
Dienogest	27 (57.5)
Norethisterone	3 (6.4)
Microlut	2 (4.3)
Drospirenone	1 (2.1)
Duration of Progestin Therapy (months): median (min-max)	12 (3-240)
Pain Symptoms before Progestin Therapy: median (min-max), VAS	9(5-10)
after Progestin Therapy: median (min-max), VAS	3(0-7)
Abnormal Uterine Bleeding	
Yes	18 (38.3)
No	29 (61.7)
Bleeding Pattern	
Cyclical	1 (5.6)
Non-Cyclical	17 (94.4)
Amount of Blood	
Same as Menstruation	1 (5.6)
Less than Menstruation	16 (88.9)
More than Menstruation	1 (5.6)

Table 1. showed that the median age of the subjects was 40 years, with an average weight of 62.4 ± 11.8 kg, height of 155.9 ± 5.6 cm, and BMI of 25.6 ± 4.6 kg/m². Of the subjects, 26 (55.3%) had endometrioma, with 15 (57.7%) being unilateral and 11 (42.3%) bilateral. The majority of subjects (42 subjects, 89.4%) had adenomyosis, and 1 subject (2.1%) had deep endometriosis lesions. A total of 22 subjects (46.8%) had a history of surgery. Most subjects (44 subjects, 93.6%) received oral progestin therapy with a median duration of 12 months (range 30-240 months), and 3 subjects (6.4%) used implants. The most commonly used oral progestins were dienogest (57.5%) and lynestrenol (23.4%). Among the 47 subjects, 18 (38.3%) experienced abnormal uterine bleeding, with 17 subjects (94.4%) having a non-cyclical bleeding pattern and 16 subjects (88.9%) experiencing bleeding less than menstruation.

Table 2. Basic Patient Characteristics Based on Pain Group

Variables	Pain (n = 24)	No Pain (n = 23)	*P-Value*
Age: Median (min-max), years	40 (27-45)	40 (25-48)	
Body Weight: Mean ± SD, kg	64 (36-96)	58 (48-85)	
Height: Mean ± SD, cm	156.2±5.9	155.6±5.4	
Body Mass Index (BMI): Mean ± SD, kg/m²	26.1 (17.6-37.5)	23.3 (20-36.3)	0.333
Endometriosis Phenotype			
Endometrioma			0.453
Yes	12 (50)	14 (60.1)	
No	12 (50)	9 (39.9)	
Endometrioma Location			0.462

Unilateral	6 (50)	9 (64.3)	
Bilateral	6 (50)	5 (35.7)	
Adenomyosis			0.600
Yes	22 (91.7)	20 (86.9)	
No	2 (8.3)	3 (13.1)	
Deep Endometriosis			0.322
Yes	1 (4.2)	0 (0.0)	
No	23 (95.8)	23 (100)	
Surgical Intervention			
Yes	12 (50)	10 (43.5)	
No	12 (50)	13 (56.5)	
Progestin Used			
Type of Medication			
Oral	24 (100)	20 (86.9)	
Implant	0 (0.0)	3 (13.1)	
Medication Type			0.067
Lynestrenol	6 (26.1)	5 (23.8)	
Dienogest	14 (60.9)	13 (61.9)	
Norethisterone	1 (4.3)	2 (9.5)	
Microlut	1 (4.3)	1 (4.8)	
Drospirenone	1 (4.3)	0 (0)	
Duration of Progestin Therapy (months): median (min-max)	8.5 (3-240)	18 (3-96)	0.849
Pain Symptoms			
before Progestin Therapy: median (min-max), VAS	9 (7-10)	9 (5-10)	0.031
After Progestin Therapy: median (min-max), VAS	4 (3-7)	1(0-2)	
Abnormal Uterine Bleeding			
Yes	9 (37.5)	9 (39.1)	
No	15 (62.5)	14 (60.9)	
Bleeding Pattern, n (%)			0.908
Cycklical	1 (11.1)	0 (0)	
Non-Cyclical	8 (88.9)	9 (100)	
Amount of Blood, n (%)			1.000
Same as Menstruation	1 (11.1)	0 (0.0)	
Less than Menstruation	7 (77.8)	9 (100)	
More than Menstruation	1 (11.1)	0 (0.0)	

The study categorized participants into two groups based on pain presence after at least 3 months of progestin therapy. The pain group had a median age of 40 years and a median weight of 64 kg, with a mean height of 156.2 cm and a median BMI of 26.1 kg/m^2. The non-pain group had a similar median age but a lower median weight of 58 kg, mean height of 155.6 cm, and median BMI of 23.3 kg/m^2, with no significant difference in BMI between groups (p = 0.333). Phenotypic analysis revealed that 50% of the pain group and 60.1% of the non-pain group had unilateral endometriomas. Adenomyosis was common in both groups (91.7% and 86.9%, respectively), while endometriosis lesions were rare, found in only 4.2% of the pain group. 50% of the pain group and 43.5% of the non-pain group had a history of surgery. Progestin therapy was predominantly oral in both groups, with all subjects in the pain group receiving oral progestin, primarily dienogest (60.9%), and 86.9% of the non-pain group also receiving oral progestin, including 61.9% on dienogest and 13.1% on implant therapy. The median duration of progestin use was shorter in the pain group (8.5 months) compared to the non-pain group (18 months). Pre-therapy, the median VAS scores were similar in both groups (9). Post-therapy, the median VAS score improved to 4 in the pain and 1 in the non-pain group. Both groups had similar rates of abnormal uterine bleeding (37.5% in the pain group and 39.1% in the non-pain group), with no significant difference (Chi-Square p = 0.908) (Table 2).

Table 3. Differences in IL-1β, IL-6, COX-2, and Estradiol Levels Based on Pain Group

Variables	Pain (n = 24)	No Pain (n = 23)	*P-Value*
IL-1β	1.54(1.15-43.12)	1.41(1.02-7.45)	0.303
IL-6	0.25(0.08-5.12)	0.29(0.09-2.01)	0.725
COX-2	1.845(1.24-10.26)	1.55(0.32-3.07)	0.004
Estradiol	47.35(17.3-314.1)	37.7(14.4-299.3)	0.587

The study compared serum levels of IL-1β, IL-6, COX-2, and estradiol between the pain and non-pain groups. Using the Mann-Whitney test, there were no significant differences in median levels of IL-1β (1.54 [1.15-43.12] vs. 1.41 [1.02-7.45], p = 0.303), IL-6 (0.25 [0.08-5.12] vs. 0.29 [0.09-2.01], p = 0.725), and estradiol (47.35 [17.3-314.1] vs. 37.7 [14.4-299.3], p = 0.587). However, a significant difference was found in COX-2 levels (1.845 [1.24-10.26] vs. 1.55 [0.32-3.07], p = 0.004) (Table 3).

Table 4. Correlation between IL-1β, IL-6, COX-2, and Estradiol

Variables		Correlation Coefficient	*P-Value*
IL-1B	Estradiol	-0.084	0.573
IL-6	Estradiol	-0.088	0.555
COX-2	Estradiol	0.035	0.817
IL-1B	IL-6	0.471	0.001
IL-1B	COX-2	0.141	0.346
IL-6	COX-2	0.045	0.766

Correlation analysis using Pearson's test evaluated the relationships between pro-inflammatory cytokines and estradiol levels. The results showed no significant correlations between IL-1β and estradiol (r = -0.084, p = 0.573), IL-6 and estradiol (r = -0.088, p = 0.555), COX-2 and estradiol (r = 0.035, p = 0.817), IL-1β and COX-2 (r = 0.141, p = 0.346), and IL-6 and COX-2 (r = 0.045, p = 0.766). However, a significant positive correlation was found between IL-1β and IL-6 (r = 0.471, p = 0.001) (Table 4 and Figure 1).

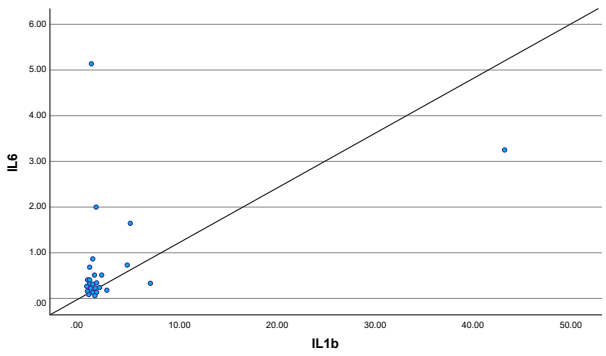

Figure 1. Correlation between IL-1β and IL-6

In this study, Pearson's correlation analysis assessed the relationships between COX-2, IL-1β, IL-6, and VAS scores. COX-2 showed a weak but statistically significant positive correlation with VAS scores (r = 0.360, p = 0.013). In contrast, IL-1β and VAS scores had a weak positive correlation that was not statistically significant (r = 0.144, p = 0.333). Similarly, IL-6 and VAS scores exhibited a weak correlation (r = 0.132, p = 0.376), and estradiol showed a weak negative correlation with VAS scores (r = -0.036, p = 0.808) (Table 5 and Figure 2).

Table 5. Correlation Between COX-2, IL-1β, IL-6, and Post-Therapy VAS ScoreS

Variables		Correlation Coefficient	*P-Value*
COX-2	VAS	0.360	0.013
IL-1B	VAS	0.144	0.333
IL-6	VAS	0.132	0.376
Estradiol	VAS	-0.036	0.808

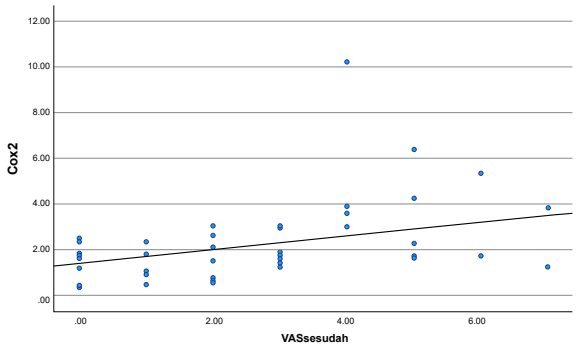

Figure 2. Correlation between COX-2 levels and post-therapy VAS scores

DISCUSSION

Dysmenorrhea, dyschezia, dyspareunia, and chronic pelvic pain are primary complaints in patients with endometriosis. Progestin is a long-term therapeutic option for managing these pains, with several studies indicating that progestin can suppress the activity of endometriosis cells and associated inflammation, thereby alleviating pain. However, the effectiveness of progestin therapy can vary, and in some cases, pain does not fully improve. This study included 47 endometriosis patients undergoing progestin therapy at RSUPN dr. Cipto Mangunkusumo. The patients were categorized into two groups: the pain and the non-pain group. The characteristics of both groups, including age, weight, height, body mass index (BMI), endometriosis phenotype, and abnormal uterine bleeding, showed no significant differences. The patients' characteristics

showed that both groups had similar baseline profiles, with a median age of approximately 40 years, consistent with the epidemiology of endometriosis in women of reproductive age, ranging from 18 to 45 years.[15] BMI also did not show a significant difference, and although biological risk factors such as BMI may be associated with endometriosis, these results align with other studies suggesting that BMI cannot be conclusively identified as a primary risk factor.[16, 17]

Before progestin therapy, the median VAS score was 9 in both groups. After treatment, the VAS score decreased to 4 in the pain group and 1 in the no pain group, consistent with several studies indicating that progestin is effective in reducing endometriosis-related pain. A meta-analysis by Mitchell et al. demonstrated that progestin improves pain symptoms (SMD = -0.61, 95% CI (-0.77, -0.45), P <0.00001). A prospective study also showed a significant reduction in VAS scores during the first three and six months of treatment. Progestin alleviates endometriosis-related pain by decreasing FSH and LH hormone secretion, leading to anovulation and reduced estrogen levels, thus inhibits the growth of endometriotic tissue through anti-inflammatory, antiproliferative, and anti-angiogenic effects, particularly by suppressing PGE2 and COX2.[18]

The study found a significant difference in COX-2 levels between the pain and non-pain groups, with median COX-2 levels being higher in the pain group compared to the non-pain group (1.845 vs. 1.55; p = 0.004). In contrast, IL-1β, IL-6, and estradiol levels did not differ significantly between the groups. This may be attributed to the localized nature of the inflammatory response in endometriosis lesions, which might not be reflected in serum levels. Endometriosis lesions can produce estrogen and elevate pro-inflammatory compounds such as IL-1β, IL-6, and COX-2.[2, 6] Although IL-6 levels increase with the extent of endometriotic tissue, IL-1β does not show a significant increase in peritoneal fluid. Serum blood tests reveal elevated IL-1β and IL-6 levels compared to controls, but there are no significant differences among various stages of endometriosis.[3]

No significant correlation was found between estradiol and the pro-inflammatory cytokines IL-1β, IL-6, and COX-2. Theoretically, estradiol can increase pro-inflammatory cytokine levels through a positive feedback mechanism,[2] however, in this study, increased estrogen may be localized to endometriosis lesions, thus not affecting serum cytokine levels. The correlations among IL-1β, IL-6, and COX-2 revealed that while IL-1β and IL-6 are correlated, there was no significant correlation between IL-1β and COX-2, or IL-6 and COX-2. This is consistent with previous studies that identified a correlation between IL-1β and IL-6 in endometriosis patients but not with COX-2. Pro-inflammatory cytokines may be more specific to endometriotic tissue rather than serum, which could explain the absence of significant correlations.[3] These findings suggest that pro-inflammatory cytokines are more specific to endometriotic tissue rather than serum blood.

The analysis indicates that COX-2 has a weak positive correlation with VAS pain scores (r=0.360; p=0.013), while no significant correlation was found between IL-1β and VAS, or IL-6 and VAS. This suggests that COX-2 may play a more significant role in the pain mechanism of endometriosis compared to IL-1β and IL-6. Chronic inflammation in endometriosis leads to alterations in pain signalling and increased sensitivity to stimuli. Inflammatory mediators such as prostaglandins, VEGF, TNF-α, NGF, and various interleukins play a role in this process. Cytokines like IL-1β and IL-6 are involved in pathological pain, with expression observed in the dorsal root ganglia and spinal cord.[6] Excessive COX-2 is associated with resistance to apoptosis and phenotypic changes in chronic diseases. COX-2 induces the production of prostaglandins, which trigger angiogenic factors such as VEGF. COX-2 expression is upregulated by IL-1β, as demonstrated in studies on colorectal cancer cells and diabetic wounds, where IL-6 levels decreased while COX-2 increased. This suggests that IL-1β in chronic pain may drive the upregulation of COX-2, explaining the significant increase in COX-2 compared to IL-1β and IL-6.[19, 20]

CONFLICT of INTEREST

The authors declare no potential conflicts of interest.

CONCLUSION

This study demonstrates that there are no significant differences in the levels of the pro-inflammatory markers IL-1β and IL-6, as well as estradiol, in the serum between endometriosis patients with and without pain who received progestin therapy. However, a significant difference was found in the COX-2 levels, which

were higher in the pain group. There was no correlation between estradiol levels and IL-1β, IL-6, or COX-2. A correlation was observed between COX-2 levels and pain intensity, and a reduction in pain intensity was noted in both groups receiving progestin therapy, as indicated by the decrease in VAS scores.

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