Research Article

Efficacy and Tolerability of Short-Term Hormonal Therapy Following Conservative Surgery for Endometriosis

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Abstract

Objective: To compare the efficacy and tolerability of four short-term hormonal therapies; Dienogest (DNG), Depot Medroxyprogesterone Acetate (DMPA), continuous Combined Oral Contraceptive (COC), and Leuprolide Acetate (LA); administered for 12 weeks after conservative endometriosis surgery.

Methods: This randomized, prospective, open-label study enrolled reproductive-aged women with surgically confirmed endometriosis. Participants were randomly assigned to receive DNG 2 mg daily, DMPA 150 mg intramuscularly every 12 weeks, continuous COC (ethinyl estradiol 0.03 mg and levonogestrel 0.15 mg) daily, or LA 3.75 mg intramuscularly every 4 weeks. Primary outcomes were changes in pain intensity (visual analog scale, VAS), hormonal markers (estradiol, E2), inflammatory markers (TNF-α), and the Menopause Rating Scale (MRS) as an indicator of tolerability. Data were analyzed using ANOVA with a significance level of $p < 0.05$.

Results: All four regimens resulted in significant reductions in dysmenorrhea, dyspareunia, and chronic pelvic pain after 12 weeks ($p < 0.001$). E2 and TNF-α levels decreased significantly in all groups, with the greatest decline observed in the LA arm. No significant differences were found among regimens in pain reduction or biomarker changes ($p > 0.05$). MRS scores increased transiently at week 8, particularly in the LA group, reflecting hypoestrogenic effects, but decreased by week 12 in all groups.

Conclusion: Short-term postoperative hormonal therapy with DNG, DMPA, COC, or LA effectively reduces pain and inflammatory markers following endometriosis surgery. Progestin-based therapies achieve comparable clinical efficacy to GnRH agonists with superior tolerability. Individualized selection based on symptom profile, side effects, and accessibility is recommended in accordance with ESHRE guidelines.

Keywords: endometriosis-associated pain, Menopause Rating Scale, short-term hormonal therapy.

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INTRODUCTION

Endometriosis is a chronic, estrogen-dependent inflammatory disorder characterized by the presence of endometrial-like tissue outside the uterine cavity, leading to pelvic pain and infertility.[1] The condition affects approximately 10% of women of reproductive age and is a major cause of chronic pelvic pain and reduced quality of life.[2] Although surgical excision of lesions can relieve symptoms and improve fertility, microscopic residual disease and local inflammation often result in recurrence and persistent pain.[3]

Postoperative hormonal therapy is essential for suppressing ovarian function, minimizing recurrence, and controlling residual pain.[4] Various regimens; including progestins, Combined Oral Contraceptives (COCs), and gonadotropin-releasing hormone (GnRH) agonists; are used to achieve hypoestrogenism and inhibit ectopic endometrial growth.[5,6] However, direct

comparative data on the short-term efficacy and tolerability of these regimens remain limited, particularly in Asian populations.

Dienogest (DNG), a fourth-generation progestin, exerts local anti-inflammatory and antiproliferative effects while maintaining stable systemic hormone levels.[7] Depot Medroxyprogesterone Acetate (DMPA) provides longer-acting progestogenic suppression but may cause menstrual irregularities and delayed fertility recovery.[8] Continuous COC regimens combine ovulation inhibition with partial estrogen replacement, offering effective pain control with fewer hypoestrogenic symptoms.[9] In contrast, GnRH agonists such as Leuprolide Acetate (LA) induce profound hypoestrogenism through pituitary desensitization, resulting in stronger pain reduction but higher rates of vasomotor and psychological effects.[10]

Inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) are implicated in the pathophysiology of endometriosis and are correlated with pain severity.[11,12] Hormonal suppression may reduce cytokine production, thereby attenuating local inflammation and neurogenic pain pathways.[13] Therefore, simultaneous assessment of endocrine and inflammatory parameters may elucidate mechanisms underlying clinical improvement.

Although long-term hormonal therapy (>6 months) has proven effective in preventing recurrence, evidence on short-term regimens is limited.[14] The present study aimed to compare the 12-week efficacy and tolerability of four commonly used hormonal regimens; DNG, DMPA, COC, and LA; after conservative surgery for endometriosis.

METHODS

This multi-arm, randomized, open-label, comparative study was approved by the Ethics Committee of the institution and conducted at Dr. Kariadi General Hospital between August 2023 and September 2024. The study adhered to the ethical principles stated in the Declaration of Helsinki and the ICH-GCP guidelines.

Eligible participants were premenopausal women between the ages of 18 and 40 who experienced endometriosis pain and did not plan to become pregnant within the next year. All participants in the study experienced pre-surgery pain levels of 5 or higher for at least one type of pain. Women were excluded from the study if they had taken any medications for endometriosis other than non-steroidal anti-inflammatory drugs in the previous six months. Participants were excluded if they had other pelvic conditions like adenomyosis, chronic pelvic inflammatory disease, or submucous uterine myoma, or if they had known gastrointestinal, urological, or orthopedic diseases. Additionally, participants were excluded if they had any contraindications to the use of DNG, DMPA, COC, or LA. Patients with mild to moderate endometriosis were treated with minimally invasive laparoscopic surgery, while those with severe endometriosis underwent open surgery. Histological examination of tissue samples was used to confirm the endometriosis diagnosis.

After obtaining written informed consent, eligible participants were randomly assigned into four treatment arms using a computer-generated randomization sequence. The study compared four short-term hormonal regimens administered for a total duration of 12 weeks. Participants in the DNG group received 2 mg orally once daily, while those allocated to the DMPA group were given 150 mg intramuscularly every four weeks. The COC group received a daily oral combination of ethinyl estradiol 0.03 mg and levonorgestrel 0.15 mg; in cases where breakthrough bleeding persisted for seven consecutive days, participants were instructed to interrupt therapy for one week before resuming treatment. The final group received LA 3.75 mg intramuscularly every four weeks. All medications were administered under standardized conditions, and adherence was monitored through pill counts at each visit to ensure treatment compliance throughout the study period.

The primary outcomes of the study were the changes in serum estradiol (E_2) and tumor necrosis factor-alpha (TNF-α) levels, the degree of pain improvement, and treatment tolerability. Pain intensity was evaluated using the Visual Analog Scale (VAS) for three domains; dysmenorrhea, dyspareunia, and chronic pelvic pain; recorded at baseline and at each follow-up visit. Tolerability was assessed using the Menopause Rating Scale (MRS), which measures vasomotor, somatic, psychological, and urogenital symptoms. Although the MRS was originally designed for peri- and postmenopausal women, it was applied in this study to objectively quantify transient hypoestrogenic symptoms induced by short-term hormonal therapy. The Indonesian-validated MRS version has shown acceptable reliability for

assessing estrogen-deficiency-related symptoms in premenopausal populations.[14] The MRS questionnaire was administered at baseline and at 4 weeks intervals. Each item is scored from 0-4; domain and total scores were calculated using standard algorithms. Higher scores indicate greater symptom severity.

In addition to these parameters, the study also documented changes in menstrual bleeding patterns and the incidence of adverse events. The bleeding patterns were characterized as Normal bleeding: regular bleeding with typical flow, frequency, and duration. Irregular bleeding: menstrual cycles shorter than 21 days or longer than 35 days. Amenorrhea: no bleeding for three months or more. Intermenstrual bleeding: Irregular bleeding between regular periods, often light and brief. The volume was estimated from self-reported sanitary product use and classified as light (<20 mL per cycle), moderate (20-40 mL), or heavy (>40 mL).

Postoperative complications (wound infection, dehiscence, localized wound pain) were recorded at the first postoperative visit and at each follow-up. Standard wound care and antibiotics were provided when indicated. Cases determined to have pain primarily attributable to surgical complications were excluded from efficacy analyses. Analgesic consumption related to wound pain was documented and adjusted for when interpreting VAS outcomes. The need for pain relief was determined based on the World Health Organization's analgesic ladder, which recommends starting with non-opioid medications such as non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen.

With a sample size of 25 patients per group, the study had an 80% chance of detecting a 15% difference between the groups, assuming a significance level of 5%. The serum levels of E_2 and TNF-α were analyzed using either ANOVA or the Kruskal-Wallis test, depending on the data distribution. The changes in continuous data (MRS and VAS scores) before and after treatment were compared using the Wilcoxon signed-rank test. All statistical tests were conducted as two-tailed tests, and p-values less than 0.05 were considered statistically significant.

RESULTS

A total of 158 cases of endometriosis were identified during the study. Of them, 105 patients met the inclusion criteria and were randomized, including 26 (27.3 %) in the DNG, 27 (28.3%) in the DMPA, 27 (28.3%) in the COC, and 25 (26.2%) in the LA group. There are three patients were lost to follow-up during the study. Baseline demographic and clinical characteristics were comparable across groups, with no significant differences in age, body mass index, stage of endometriosis, parity, or baseline pain scores ($p > 0.05$). (Table 1).

Table 1. Patient Demographics and Pretreatment Characteristics

Characteristics	Dienogest (n=26)	DMPA (n=27)	COC (n=27)	LA (n=25)	*P-value*
Age, years (mean ± SD)	29.2 ± 4.5	31.7 ± 4.0	30.5 ± 3.5	29.4 ± 2.4	0.06
BMI (mean ± SD)	22.7 ± 3.3	23.1 ± 3.0	23.4 ± 4.0	22.9 ± 4.0	0.93
Unilateral endometrioma n (%)	17 (65.4)	13 (48.1)	15 (55.6)	17 (68.0)	0.43
Bilateral endometrioma n (%)	9 (34.6)	14 (51.9)	12 (44.4)	8 (32.0)	
rASRM stage n (%)					
Stage III	11 (42.3)	11 (40.7)	11 (40.7)	10 (40.0)	0.99
Stage IV	15 (57.7)	16 (59.3)	16 (59.3)	15 (60.0)	
Procedure n (%)					
Cystectomy	22 (84.6)	20 (74.1)	23 (85.2)	22 (88.0)	0.55
Oophorectomy	4 (15.4)	7 (25.9)	4 (14.8)	3 (12.0)	

Hormonal and Inflammatory Markers

Table 2 presents that at the baseline, serum 17β-estradiol and TNF-α levels were comparable among the four treatment groups ($p = 0.455$ and $p = 0.239$, respectively). After 12 weeks of therapy, all regimens produced a statistically significant decline in both endocrine and inflammatory biomarkers, reflecting the combined suppressive and anti-inflammatory actions of postoperative hormonal therapy.

For estradiol, the most profound suppression was observed in the LA group, in which mean levels fell from 194.0 ± 48.6 pg/mL to 26.2

± 12.4 pg/mL ($p < 0.001$), representing an approximate 88 % reduction. The DMPA and DNG groups showed moderate reductions (-69 % and -63 %, respectively), whereas the COC group showed a milder decline (-53 %). Between-group analysis confirmed that post-treatment estradiol levels differed significantly ($p < 0.001$), with LA producing the greatest ovarian suppression. These findings are consistent with the pharmacodynamic profiles of the agents, where GnRH agonists achieve near-complete pituitary down-regulation and progestins exert partial inhibition of gonadotropin secretion. [4-6]

Similar trends were seen for TNF-α. Median baseline values ranged from 2.6 to 5.0 pg/mL and decreased in all groups by week 12, reaching medians between 1.5 and 1.8 pg/mL. The within-group changes were statistically significant ($p < 0.01$), but inter-group differences were not ($p = 0.651$). The consistent decline across regimens indicates that hormonal suppression attenuates systemic inflammation regardless of mechanism.

Table 2. Changes in Serum Estradiol (17β-estradiol) and Tumor Necrosis Factor-α (TNF-α) Levels after 12 Weeks of Treatment

Parameter	Group	Baseline (mean/median ± SD or IQR)	Post-treatment (mean/median ± SD or IQR)	*P-value* (within group)	*P-value* (between groups)
17β-estradiol (pg/mL)	DNG (n=21)	190.6 ± 60.8	71.3 ± 30.0	<0.001	
	DMPA (n=20)	203.4 ± 67.9	62.5 ± 23.6	<0.001	
	COC (n=20)	174.7 ± 43.1	82.9 ± 36.8	<0.001	
	LA (n=20)	194.0 ± 48.6	26.2 ± 12.4	<0.001	0.455 (baseline), <0.001† (post)
TNF-α (pg/mL)	DNG (n=21)	3.3 (2.2-14.8)	1.5 (1.1-2.3)	<0.01	
	DMPA (n=20)	2.6 (1.6-8.6)	1.54 (1.1-3.0)	<0.01	
	COC (n=20)	5.0 (1.9-10.9)	1.8 (1.3-3.1)	<0.01	
	LA (n=20)	4.4 (2.9-10.8)	1.7 (1.3-2.7)	<0.01	0.239† (baseline), 0.651† (post)

Values are presented as mean ± SD for normally distributed data and median (IQR) for skewed distributions.
†p-values represent between-group comparisons by one-way ANOVA or Kruskal-Wallis test, as appropriate.

Pain Perception

At baseline, median Visual Analog Scale (VAS) scores for dysmenorrhea, dyspareunia, and chronic pelvic pain were comparable across the four treatment groups ($p > 0.05$), indicating balanced pain severity before intervention (Table 3). After 12 weeks of therapy, all groups exhibited significant improvement in pain perception ($p < 0.001$ for all within-group comparisons).

For dysmenorrhea, median VAS scores decreased from 6 (IQR 5-8) at baseline to 0.3 (IQR 0-1.1) in the DNG group, from 6 (IQR 5-8) to 0 (IQR 0-0) in both DMPA and COC groups, and from 6 (IQR 5-7) to 0 (IQR 0-0) in the LA group. Similar patterns were observed for dyspareunia, with median scores declining from 3.0 (IQR 2.2-4.1) to 0 (IQR 0-0.7) in DNG users, and from approximately 3.0 to 0 in the other treatment arms. Chronic pelvic pain also resolved substantially, decreasing from baseline medians of 3.4-4.3 to 0 across all groups.

The magnitude of improvement was greatest within the first 8 weeks, followed by continued stabilization by week 12. Although intergroup comparisons did not reveal statistically significant differences ($p > 0.05$), the uniform reduction in VAS scores across all arms demonstrates that each regimen; DNG, DMPA, COC, and LA; achieved equivalent efficacy in relieving endometriosis-associated pain following conservative surgery.

Table 3. Comparison of the VAS Pain Score Across the Groups at Baseline and Twelve weeks of Treatment

Endometriosis Pain (VAS score)	Baseline median (IQR)	Twelve weeks of treatment median (IQR)
Dysmenorrhea		
DNG (n=26)	6 (5-8)	0.3 (0-1.1)
DMPA (n=27)	6 (5-8)	0 (0-0)
COC (n=27)	6 (5-8)	0 (0-0.5)
LA (n=25)	6 (5-7)	0 (0-0)
Dyspareunia		
DNG (n=26)	3 (2.2-4.1)	0 (0-0.7)
DMPA (n=27)	2.9 (1.8-4.9)	0 (0-0)
COC (n=27)	3.2 (1.9-4.5)	0 (0-0.5)
LA (n=25)	3.4 (2-5.1)	0 (0-0)
Pelvic pain		
DNG (n=26)	4 (2.7-5.3)	0 (0-0.4)
DMPA (n=27)	3.4 (2.4-5.1)	0 (0-0)
COC (n=27)	3.4 (2.5-5)	0 (0-0.5)
LA (n=25)	4.3 (2.9-5.3)	0 (0-0)

Tolerability and Menopause Rating Scale (MRS) Scores

During the 12 weeks observation period, all treatment groups experienced a characteristic biphasic trend in Menopause Rating Scale (MRS) scores. The total MRS initially increased by week 8, reflecting transient hypoestrogenic symptoms, but subsequently declined by week 12, suggesting adaptive symptom improvement as hormonal equilibrium was restored. The LA group demonstrated the most pronounced fluctuation, with mean total MRS scores rising from 7.9 ± 1.6 at week 4 to 22.6 ± 5.9 at week 8, followed by a reduction to 6.7 ± 3.1 at week 12 ($p < 0.0001$). In comparison, women receiving progestin-based regimens showed milder variations. The DNG group recorded mean scores of 7.3 ± 2.0, 10.9 ± 6.0, and 5.4 ± 2.7 at weeks 4, 8, and 12 respectively ($p < 0.0001$), while the DMPA and COC groups exhibited similar mid-course increases to 15.5 ± 4.9 and 14.2 ± 4.0 at week 8, followed by declines to 6.1 ± 3.0 and 5.9 ± 3.2 at week 12 ($p < 0.0001$ for both). Between-group analysis confirmed significant differences at week 8 ($p < 0.0001$), predominantly due to the higher symptom burden in the LA arm, but no significant differences persisted by week 12 ($p = 0.516$).

Component analysis of the MRS further clarified the tolerability profiles among regimens. Vasomotor symptoms such as hot flushes were most prominent in LA users, with mean scores of 2.6 ± 1.2 compared to 1.2 ± 0.8 in the DNG group, 1.6 ± 1.0 in DMPA, and 1.1 ± 0.9 in COC users ($p < 0.001$). Sleep disturbance followed a similar pattern, peaking at 2.9 ± 1.3 in the LA arm and remaining between 1.4 and 1.9 in the progestine and COC groups ($p < 0.001$). Psychological and urogenital complaints were likewise more frequent among LA recipients, averaging 2.1 ± 1.0 and 1.9 ± 0.9 respectively, whereas somatic complaints showed no significant variation between groups ($p = 0.08$).

Overall, the transient increase in total and component MRS scores among LA users represents a predictable hypoestrogenic response to GnRH agonist therapy, while the milder and shorter-lived symptoms in DNG, DMPA, and COC recipients indicate better tolerability. These results confirm that progestin-based therapies offer comparable efficacy to GnRH agonists with a more favorable side-effect profile, supporting their suitability for short-term postoperative management of endometriosis.

Adverse Effect and Bleeding Patterns

No serious or unexpected adverse events occurred during the 12 weeks treatment period, and no participant discontinued therapy due to side effects. The most frequent complaint was a change in bleeding pattern, followed by mild headache, breast tenderness, nausea, and occasional weight gain. Headache was more frequent in the LA group (20%) than in COC (11.2%), DMPA (7.4%), or DNG users (3.8%). Weight gain occurred only in the DMPA group (3.7%), consistent with its progestogenic metabolic profile. Non-bleeding adverse effects were mild and transient. Headache and breast tenderness resolved spontaneously, and nausea reported by 7.4% of COC users and 7.6% of DNG users typically abated after the first month. No thromboembolic events or significant blood pressure elevations were recorded in COC users.

Bleeding disturbances were common across all regimens and represented a predictable pharmacologic effect rather than an adverse reaction requiring discontinuation. After 16 weeks, the proportion of women with normal cyclic bleeding decreased substantially in all groups, (DNG 73.1 to 23.1%; DMPA 81.5 to 0%; COC 77.8 to 22.2%; and LA group 76 to 0%). Correspondingly, amenorrhea rates rose, particularly among DMPA (0% to 48%) and LA users (0% to 88%), whereas intermenstrual spotting increased modestly in all groups (ranging 7-18%). These findings reflect the degree of ovarian suppression achieved by each regimen, with GnRH agonist therapy producing the most hypoestrogenic state.

DISCUSSION

All four hormonal regimens; dienogest (DNG), Depot Medroxyprogesterone Acetate (DMPA), continuous Combined Oral Contraceptive (COC), and Leuprolide Acetate (LA); showed comparable efficacy in reducing endometriosis-associated pain following conservative surgery. This finding supports the concept that suppression of ovarian activity, regardless of the pharmacologic mechanism, effectively alleviates the endocrine and inflammatory processes responsible for pain in endometriosis.[8,13] The improvement in dysmenorrhea, dyspareunia, and chronic pelvic pain observed in this study is consistent with previous reports demonstrating that

postoperative hormonal therapy provides both rapid and sustained pain relief.[6,9,10]

Serum estradiol (E_2) levels decreased significantly across all treatment groups, with the most profound suppression seen among LA users. GnRH agonists such as leuprolide acetate induce pituitary desensitization and a hypoestrogenic state, producing strong pain relief but a higher incidence of vasomotor symptoms.[4,5] In contrast, progestin-based therapies such as DNG and DMPA achieve partial suppression of estrogen while maintaining better tolerability.[7,14] The comparable magnitude of pain reduction among regimens in this study reinforces the view that full estrogen deprivation is not necessary to achieve meaningful symptom control.[10,15]

The consistent decline in TNF-α levels across treatment groups further supports the anti-inflammatory role of hormonal therapy in endometriosis. TNF-α is a key cytokine implicated in macrophage activation, angiogenesis, and nociceptive sensitization.[15,16] Hormonal suppression significantly reduces TNF-α and interleukin-6 concentrations after surgery, reflecting attenuation of both systemic and local inflammation.[17,18] These findings confirm that both GnRH agonists and progestin-based regimens share a common immunomodulatory mechanism through suppression of estrogen-dependent inflammatory pathways.[19,20]

In terms of tolerability, the transient increase in total MRS scores observed around week 8 corresponds to the temporary hypoestrogenic effects commonly reported with hormonal therapy. Vasomotor instability and sleep disturbances are expected dose-dependent reactions to estrogen withdrawal, most prominent among GnRH agonist users.[21,22] Improvement in MRS scores by week 12 in this study mirrors previously documented adaptive recovery of the neuroendocrine axis after continued therapy.[23] DNG and COC demonstrated the most favorable tolerability, aligning with prior findings that these regimens maintain quality of life through balanced hormonal modulation.[11,12]

DMPA produced intermediate results, with mild weight gain and reversible amenorrhea as previously described.[16-18] The DMPA mechanism of estradiol suppression is consistent with the ECHO trial findings, showing dose-dependent ovarian quiescence during therapy.[16] Mild weight gain and temporary menstrual disturbances are recognized consequences of prolonged medroxyprogesterone exposure, as confirmed by systematic reviews and pharmacokinetic data.[17,18]

No serious adverse events were reported during the study, confirming the favorable safety profile of all four regimens.[14,19] Bleeding irregularities and amenorrhea were common pharmacologic effects rather than adverse reactions requiring discontinuation, consistent with the expected endocrine suppression pattern.[24,25] Progestin-based regimens thus appear to provide an optimal balance between efficacy, tolerability, and safety, particularly where cost or hypoestrogenic symptoms limit prolonged GnRH agonist use.[4,9]

The comparable efficacy of these treatments highlights that consistent ovarian suppression, rather than the specific pharmacologic agent, is the main determinant of postoperative pain control. This conclusion is consistent with the ESHRE guidelines, which recommend individualized therapy according to patient symptoms, fertility intentions, and tolerance.[2,3] Additional evidence supports the benefit of combining endocrine and inflammatory pathway modulation to optimize outcomes and reduce recurrence.[20,26]

The present study is limited by its short duration of 12 weeks, which precludes assessment of long-term recurrence or quality-of-life outcomes. Previous studies indicate that continuous hormonal suppression for six months or longer provides more durable symptom relief and lowers recurrence rates.[10,19] Future research should explore extended regimens and evaluate their effects on recurrence, bone density, and fertility outcomes. Biomarker and imaging-based follow-up, as proposed in recent translational studies, could further elucidate molecular predictors of treatment success.[19,27]

In summary, short-term postoperative hormonal therapy with DNG, DMPA, COC, or LA effectively reduces pain and inflammatory markers after conservative surgery for endometriosis. Progestin-based therapies demonstrate equivalent clinical benefit to GnRH agonists with superior tolerability and minimal side effects. Treatment should be tailored to the patient's symptom profile, adverse effect tolerance, and accessibility of therapy, in accordance with current ESHRE recommendations.[2]

CONCLUSION

Short-term postoperative hormonal therapy with dienogest, depot medroxyprogesterone acetate, continuous combined oral contraceptives,

or leuprolide acetate provides significant and comparable reductions in pain and inflammatory activity following conservative surgery for endometriosis. All regimens effectively suppress estradiol and TNF-α levels, leading to meaningful symptom improvement within 12 weeks.

Progestine-based therapies offer clinical efficacy equivalent to GnRH agonists while demonstrating superior tolerability and fewer hypoestrogenic adverse effects, making them suitable first-line options for postoperative management. The choice of regimen should be individualized according to patient symptom severity, tolerance, and resource accessibility. Further studies with longer follow-up are warranted to evaluate recurrence rates, fertility outcomes, and long-term quality of life.

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