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Health-Related Quality of Life and Pain Outcomes Following Surgery and Postoperative Hormonal Therapy for Advanced Endometriosis: A Prospective Cohort Study of Recovery and Treatment Outcomes

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Abstract

Background: Advanced endometriosis substantially impairs health-related quality of life (HRQoL). This prospective cohort study assessed six-month changes in HRQoL and pain following surgical treatment and postoperative hormonal therapy and explored whether postoperative changes and adverse-effect profiles differed according to hormonal treatment. **Methods**: Fifty women with histologically confirmed rASRM stage III–IV endometriosis underwent surgical treatment. SF-36v2 and Numerical Rating Scale (NRS) scores were assessed preoperatively and at six months. Paired changes, correlations with pain reduction, disease-stage differences, and exploratory comparisons among dienogest, GnRH-agonist, and combined ethinylestradiol/dienogest (EE/DNG) treatment groups were analysed. Adverse effects were compared using the Fisher–Freeman–Halton exact test with Holm adjustment. **Results**: All eight SF-36v2 domains improved significantly (all $p < 0.001$; r = 0.74–0.87), and median NRS pain decreased from 8 (IQR 7–8) to 2 (IQR 1–3) ($p < 0.001$; r = 0.87). Pain reduction was positively associated with improvement across all SF-36v2 domains; seven of eight correlations were statistically significant before adjustment, while four remained significant after Holm correction, with the strongest association observed for Bodily Pain ($\varrho = 0.538$). No statistically significant differences in pain or HRQoL change were detected by rASRM stage or postoperative hormonal regimen. Hot flushes differed across hormonal groups and were most frequent with GnRH-agonist therapy (56.3%; Holm-adjusted $p = 0.010$). **Conclusions**: Six months after surgery and postoperative hormonal therapy for advanced endometriosis, substantial improvements in HRQoL and pain were observed. HRQoL improvement was only partly associated with pain reduction. Exploratory comparisons among postoperative hormonal regimens did not detect differences in patient-reported improvement, whereas tolerability profiles differed, particularly with respect to hot flushes in the GnRH-agonist group. Because treatment allocation was not randomized, these findings do not establish comparative efficacy or treatment equivalence.

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Keywords: endometriosis; health-related quality of life; SF-36v2; pelvic pain; patient-reported outcomes; endometriosis surgery; HRQoL

1. Introduction

Endometriosis is a chronic, estrogen-dependent inflammatory disease characterized by the presence of endometrial-like glands and stroma outside the uterine cavity [1]. It affects approximately 10% of women of reproductive age and is diagnosed in up to 30–50% of women with infertility and nearly half of those suffering from chronic pelvic pain [1]. The clinical presentation is highly heterogeneous, with dysmenorrhea, chronic pelvic pain, dyspareunia, and infertility representing the most common manifestations [1–3]. Delayed diagnosis contributes to disease progression, chronic pain, impaired fertility, psychological distress, and substantial deterioration in HRQoL [1,3–5]. Over the past decade, HRQoL has become one of the principal outcomes in the management of endometriosis [5–8]. While pain relief and fertility preservation remain major therapeutic goals, increasing attention has been directed toward the impact of treatment on physical functioning, emotional well-being, social relationships, work productivity, and sexual health. Numerous studies have demonstrated that chronic pelvic pain, dyspareunia, fatigue, infertility, anxiety, and depression are among the strongest determinants of reduced quality of life in women with endometriosis [9–11]. Consequently, patient-reported outcome measures are increasingly incorporated into both clinical practice and research to evaluate treatment effectiveness from the patient's perspective [5,6,8,9,12].

Several validated instruments are available for assessing HRQoL in women with endometriosis. Disease-specific tools, particularly the Endometriosis Health Profile-30 (EHP-30), evaluate the multidimensional burden of the disease, whereas generic questionnaires such as the Medical Outcomes Study Short Form-36 version 2 (SF-36v2) enable comparisons across different chronic conditions [8,13,14]. Although disease-specific questionnaires provide greater sensitivity to endometriosis-related symptoms, the SF-36 remains one of the most extensively validated generic HRQoL instruments and facilitates comparisons across different chronic diseases, populations, and therapeutic interventions [13]. Consequently, the SF-36 has been widely used to evaluate health-related quality of life following surgical treatment for endometriosis [5,10,14–16].

Surgical treatment remains an essential therapeutic option for women with moderate-to-severe endometriosis, particularly those with deep infiltrating endometriosis (DIE), persistent pain despite medical therapy, organ involvement, or infertility [1–3,17,18]. The primary objectives of surgery include complete excision of endometriotic lesions, restoration of normal pelvic anatomy, pain reduction, and preservation or improvement of reproductive potential [1,2,17]. Previous studies and systematic reviews have demonstrated significant postoperative improvements in HRQoL following surgical treatment for endometriosis [10,14–16,19–22]. Improvements are consistently most pronounced in pain relief, physical functioning, emotional well-being, and social participation [5,7,9,10,12,13,15,16,20,22,23].

Beyond pain relief, increasing evidence suggests that surgical treatment may positively influence sexual function [2,12]. Dyspareunia is one of the most disabling symptoms of endometriosis and contributes substantially to impaired intimate relationships, reduced sexual satisfaction, and diminished quality of life [1–3,12]. Successful surgical excision of endometriotic lesions has been associated with reduced dyspareunia, improved sexual function, and enhanced quality of life [2,12]. Nevertheless, the relationship between postoperative improvements in quality of life, sexual function, and reproductive outcomes remains insufficiently investigated and requires further study [2,17].

The present study aimed to prospectively evaluate six-month changes in HRQoL after surgical treatment for advanced endometriosis using the SF-36v2 questionnaire, quantify changes in pain intensity, and examine the association between pain reduction and improvement in individual SF-36v2 domains. Secondary exploratory objectives were to assess whether postoperative changes differed according to rASRM stage or postoperative hormonal regimen and to compare adverse-effect profiles across the three main hormonal treatment groups. We hypothesized that surgery followed by postoperative management would be associated with substantial improvements in pain and HRQoL, while exploratory hormonal-regimen analyses might reveal differences in tolerability.

2. Materials and Methods

2.1. Study Design and Participants

This prospective observational cohort study evaluated changes in health-related quality of life following surgical treatment and subsequent hormonal therapy for advanced (stage III–IV) endometriosis. Women of reproductive age who underwent surgical treatment for histologically confirmed endometriosis at the Department of Gynecology, Independent Public Clinical Hospital No. 1, Pomeranian Medical University in Szczecin, Poland, between February 2024 and December 2025 were eligible for inclusion. Recruitment and surgical treatment took place between February 2024 and December 2025, with the last participant undergoing surgery in December 2025. Postoperative follow-up was scheduled for six months after surgery, corresponding to the planned six-month postoperative hormonal treatment period (Figure 1).

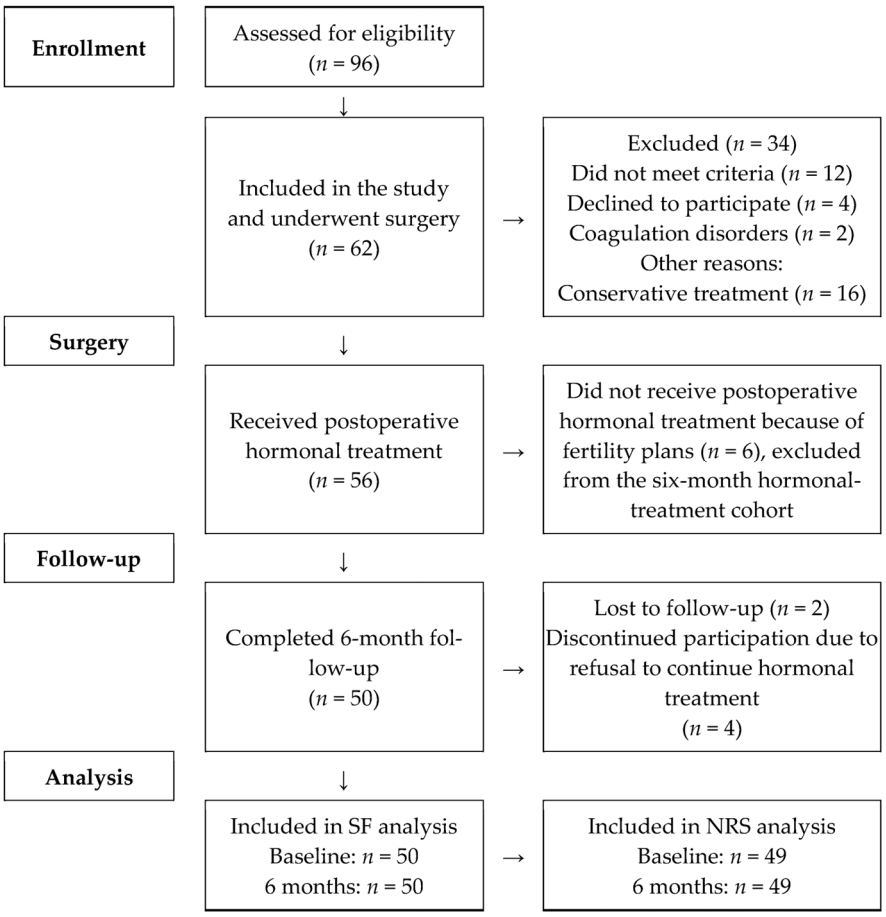


Figure 1. Participant flow diagram.

Participants were recruited consecutively during the study period. All patients presenting to the Department of Gynecology who met the predefined eligibility criteria were assessed for participation and were included according to the order of presentation.

Patients were included if they were ≥18 years of age, had surgically and histopathologically confirmed stage III or IV endometriosis according to the revised American Society for Reproductive Medicine (rASRM) classification, and completed preoperative and six-month postoperative assessments. Participants with available baseline and six-month postoperative assessments during postoperative hormonal treatment were included in the study. The postoperative assessment was scheduled for six months after surgery, corresponding to the planned six-month postoperative hormonal treatment period. Because the exact dates of the individual follow-up visits were not systematically recorded, the actual interval between surgery and assessment could not be calculated retrospectively. Outcome-specific analyses were performed using available paired observations. Complete paired data were available for 50 participants in seven SF-36v2 domains and for 49 participants in the General Health domain and NRS pain intensity. Missing values were not imputed (Supplementary Table S1).

The study was approved by the Institutional Bioethics Committee of the Pomeranian Medical University (approval No KB-006/05/2024) and all participants provided written informed consent prior to enrolment.

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies.

2.2. Clinical Assessment

Baseline demographic and clinical characteristics were collected prospectively from medical records. Variables included age, body mass index (BMI), parity, infertility history, serum anti-Müllerian hormone (AMH) concentration (when available), and disease stage according to the revised American Society for Reproductive Medicine (rASRM) classification.

Intraoperative findings included the anatomical distribution of endometriotic lesions and the type of surgical procedure performed. Surgical treatment was performed by laparoscopy or laparotomy, as clinically appropriate. Procedures included ovarian cystectomy, adhesiolysis, coagulation or ablation of endometriotic lesions, excision of endometriotic lesions from the pouch of Douglas, oophorectomy or adnexectomy, myomectomy, and salpingectomy, either alone or in combination, depending on the intraoperative findings. The extent and type of surgery were determined according to intraoperative findings, with the aim of treating visible endometriotic lesions while preserving pelvic organ function whenever clinically appropriate.

2.3. Quality-of-Life Assessment

Health-related quality of life (HRQoL) was assessed preoperatively and at the six-month postoperative follow-up using the validated Polish-language version of the Medical Outcomes Study Short Form-36 (SF-36v2) [24]. The questionnaire comprises eight domains: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH). Domain scores were calculated according to the original SF-36v2 scoring algorithm and transformed to a 0–100 scale, with higher scores indicating better HRQoL. Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were not calculated because the analyses focused on individual domains [24,25].

Complete paired observations were available for all 50 participants in seven SF-36v2 domains and for 49 participants in the General Health domain because one baseline

General Health score was unavailable. No missing values were imputed, and outcome-specific analyses were based on available observations (Supplementary Table S1).

2.4. Pain Assessment

Pain intensity was evaluated using the 11-point Numerical Rating Scale (NRS), ranging from 0 (no pain) to 10 (worst imaginable pain). Patients completed the NRS questionnaire before surgery and at postoperative follow-up.

2.5. Postoperative Hormonal Treatment and Adverse-Effect Assessment

Postoperative hormonal treatment was selected from the available regimens according to clinical considerations, contraindications, reproductive plans, and patient preference. All 50 participants received postoperative hormonal treatment; no participant elected to attempt conception immediately after surgery without postoperative hormonal suppression. No treatment switching, temporary interruption, or permanent discontinuation occurred during the six-month study follow-up. All participants maintained their prescribed postoperative hormonal regimen until completion of the six-month assessment.

For exploratory between-group analyses, participants were classified according to their postoperative hormonal regimen. Treatment modifications reported after the six-month follow-up assessment were not included in the study outcomes. The stability of treatment exposure in the three principal hormonal treatment groups is summarized in Supplementary Table S4.

Dienogest was administered as Visanne 2 mg orally once daily, beginning on the first day of the first menstrual cycle after surgery and continued without a hormone-free interval. Combined EE/DNG (Atywia) was likewise started on the first day of the next menstrual cycle and administered continuously. Triptorelin (Diphereline SR 3.75 mg) was initiated by intramuscular injection on days 2–5 of the first postoperative menstrual cycle and repeated every 28 days for up to 6 months. Some patients subsequently underwent treatment modification because of adverse effects, including persistent spotting during dienogest therapy. These modifications occurred only after the six-month follow-up visit and were outside the predefined study observation period.

The principal GnRH-agonist used was triptorelin (Diphereline SR 3.75 mg), administered by intramuscular injection every 28 days. Three patients received Ryeqo, an oral GnRH-antagonist-based combination containing built-in add-back therapy, and one patient received medroxyprogesterone acetate (Provera), a synthetic progestogen. Because these regimens were used in substantially smaller numbers and differed pharmacologically from the three principal postoperative hormonal regimens, these four patients were classified as the "Other" group and excluded from between-group analyses of treatment outcomes and adverse effects.

Adverse effects were assessed during follow-up at approximately 1, 3, and 6 months after surgery. No formal adverse-effect questionnaire or predefined symptom checklist was used. At each assessment, patients were asked about treatment-related adverse effects, and reported symptoms were recorded in the study file. A single participant could report more than one adverse effect; therefore, adverse-effect categories were not mutually exclusive. For the analysis, adverse effects recorded at the 1-, 3-, and 6-month assessments were considered over the entire 6-month follow-up period rather than only at the final 6-month visit.

For the adverse-effect analysis, participants were classified according to the postoperative hormonal regimen prescribed after surgery and maintained throughout the six-month follow-up period.

2.6. Outcomes

The primary outcome was the within-participant change in HRQoL from the preoperative assessment to six-month postoperative follow-up across the eight SF-36v2 domains. Secondary outcomes were change in NRS pain intensity and the association between pain reduction and SF-36v2 improvement. Comparisons according to rASRM stage and postoperative hormonal regimen, as well as adverse-effect comparisons, were prespecified as exploratory analyses and were not designed or powered to establish comparative efficacy, equivalence, or non-inferiority between treatment groups.

2.7. Statistical Analysis

No a priori sample-size calculation was performed. The sample size was determined by the number of eligible participants recruited during the study period who fulfilled the inclusion criteria and completed the required follow-up assessments. Analyses according to postoperative hormonal treatment were exploratory and were not powered to establish equivalence or non-inferiority between treatment regimens.

Continuous variables were assessed for normality using the Shapiro–Wilk test.

Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate, whereas categorical variables are expressed as frequencies and percentages. Outcome-specific analyses were performed using available observations. Paired analyses included only participants with valid scores at both assessment points for the corresponding outcome. Missing data were not imputed. The numbers of available baseline, follow-up, and paired observations for each outcome are provided in Supplementary Table S1.

Pre- and postoperative SF-36v2 and NRS scores were compared using the Wilcoxon signed-rank test. Effect sizes (r) were calculated for each comparison. To account for multiple testing across the eight SF-36v2 domains, Holm–Bonferroni correction was applied. Bootstrap 95% confidence intervals were calculated for the median changes (Δ) in SF-36 domain scores and NRS pain intensity using 10,000 bootstrap resamples with replacement and the percentile method.

ΔNRS was defined as preoperative NRS minus postoperative NRS, so positive values indicate pain reduction; ΔSF-36 was defined as postoperative minus preoperative score, so positive values indicate HRQoL improvement.

Spearman's rank correlation coefficients were calculated to evaluate associations between reductions in pain intensity (ΔNRS) and improvements in SF-36v2 scores (ΔSF-36). Holm–Bonferroni correction was applied to the eight correlation tests to account for multiple comparisons. Differences in treatment response between women with stage III and stage IV endometriosis were analysed using the Mann–Whitney U test. Holm adjustment was additionally applied within the family of exploratory rASRM-stage outcome comparisons.

Differences in change scores among the three main postoperative hormonal treatment groups were analysed using the Kruskal–Wallis test. These analyses were exploratory and were not interpreted as tests of treatment equivalence. Baseline characteristics of the three principal postoperative hormonal treatment groups were summarized descriptively to assess potential baseline imbalance and the possibility of selection bias or confounding by indication. Variables included age, BMI, rASRM stage, infertility history, baseline NRS pain intensity, and baseline scores for all eight SF-36 domains. Given the exploratory nature of this assessment and the small subgroup sizes, emphasis was placed on descriptive statistics rather than multiple significance tests across baseline variables. Because treatment allocation was non-randomized, unadjusted between-group comparisons of ΔNRS and ΔSF-36 may be influenced by baseline differences between treatment groups. Holm adjustment was additionally applied within the family of exploratory

postoperative hormonal-regimen outcome comparisons. As a sensitivity analysis, baseline-adjusted comparisons of six-month outcomes among the three principal hormonal treatment groups were performed using analysis of covariance (ANCOVA), with treatment group as a fixed factor and the corresponding baseline outcome score as a covariate (Supplementary Table S3). In additional analyses, changes over time were assessed using separate linear mixed-effects models with patient-specific random intercepts, adjusting for age and rASRM stage (Supplementary Table S9). The linear mixed-effects models were estimated using restricted maximum likelihood (REML), with Satterthwaite's approximation used to determine degrees of freedom. Separate models were fitted for each SF-36v2 domain and NRS pain intensity, including assessment time, age, and rASRM stage as fixed effects and a participant-specific random intercept. The analyses were based on available complete paired observations, without imputation of missing values (Supplementary Table S9).

The distribution of adverse effects across the three main postoperative hormonal treatment groups was compared using the Fisher–Freeman–Halton exact test, with Holm adjustment applied for multiple comparisons. When the global comparison for an adverse effect remained statistically significant after multiplicity adjustment, exploratory pairwise Fisher exact tests were performed, with Holm adjustment applied across the three pairwise comparisons. The other hormonal treatment group was excluded from between-group comparisons because of its small and heterogeneous composition (n = 4).

A two-sided p value < 0.05 was considered statistically significant. Statistical analyses were performed using TIBCO Statistica version 14.1.04 (TIBCO Software Inc.) and R statistical software benefits [4.4.0.] within the RStudio environment. The emmeans package in R was used to estimate adjusted marginal means and their 95% confidence intervals for the ANCOVA models.

3. Results

3.1. Baseline Characteristics of the Study Population

A total of 50 women who underwent surgical treatment for histologically confirmed stage III or IV endometriosis and subsequent hormonal therapy were included in the study. Because of a small number of missing outcome scores, the number of observations differed slightly between individual analyses. Baseline demographic and clinical characteristics are summarized in Table 1. The mean age of the participants was 32.38 ± 5.91 years, and the median body mass index (BMI) was 23.6 kg/m² (IQR, 20.3–26.8). According to the revised American Society for Reproductive Medicine (rASRM) classification, 37 women (74.0%) had stage IV disease and 13 (26.0%) had stage III disease. Disease stage was available for all 50 participants.

Table 1. Baseline demographic and clinical characteristics of the study population.

Variable	Value
Number of participants, *n*	50
Age (years), mean ± SD	32.38 ± 5.91
BMI (kg/m²), median (IQR)	23.6 (20.3–26.8)
AMH (ng/mL), mean ± SD (n = 30)	3.67 ± 2.21
rASRM stage, *n* (%)	
Stage III	13 (26.0)
Stage IV	37 (74.0)
Parity, n (%)	
0	33 (66.0)
1	13 (26.0)
2	3 (6.0)

3	1 (2.0)
History of infertility, *n* (%)	8 (16.0)
Preoperative treatment, *n* (%)	14 (28.0)

AMH measurements were available for 30 participants. Complete-case analysis was performed for variables with missing data. One participant had missing information regarding history of infertility.

The distribution of endometriosis lesions according to the Enzian classification is presented in Table 2 [19]. Adenomyosis (Enzian FA1) was documented by ultrasonography in 27 of 50 participants (54.0%), while 23 participants (46.0%) were classified as FA0. The Enzian classification was used to characterize the anatomical distribution and extent of endometriotic lesions, including involvement of the rectovaginal space (A), uterosacral ligaments and pelvic sidewall (B), and rectum/rectosigmoid (C), as well as adenomyosis (FA), bladder (FB), other intestinal sites (FI), and ureteral involvement (FU).

Table 2. Distribution of Endometriosis Lesions According to the Enzian Classification.

Surgical Enzian		**N (%)**
P (peritoneum)	0	0 (0%)
	1	15 (30%)
	2	28 (56%)
	3	7 (14%)
O (Ovary) L/R	0	0 (0%)
	1	0 (0%)
	2	27 (54%)
	3	23 (46%)
T (Tube) L/R	0	0 (0%)
	1	7 (14%)
	2	20 (40%)
	3	23 (46%)
A (rectovaginal space)	0	43 (86%)
	1	5 (10%)
	2	2 (4%)
	3	0 (0%)
B (Uterosacral ligaments, cardinal, pelvic side walls) L/R	0	12 (24%)
	1	27 (54%)
	2	11 (22%)
	3	0 (0%)
C (rectum)	0	50 (100%)
	1	0 (0%)
	2	0 (0%)
	3	0 (0%)
FA (adenomyosis)	0	23 (46%)
	1	27 (54%)
FB (bladder)	0	50 (100%)
FI (intestinum)	0	50 (100%)
FU (ureter)	0	50 (100%)
F Diaphragm	0	50 (100%)

Surgical characteristics are presented in Table 3. Ovarian cystectomy was the most frequently performed procedure (92%), followed by adhesiolysis (50%) and coagulation or ablation of endometriotic lesions (40%). Less common procedures included Douglas

pouch endometriosis excision, oophorectomy/adnexectomy, myomectomy, and salpingectomy.

Table 3. Surgical Enzian.

Variable	n (%)
Laparoskopia	31 (62%)
Laparotomia	19 (38%)
Ovarian cystectomy (unilateral or bilateral)	46 (92%)
Adhesiolysis	25 (50%)
Coagulation/ablation of endometriotic lesions	20 (40%)
Douglas pouch endometriosis excision	4 (8%)
Oophorectomy/adnexectomy	3 (6%)
Myomectomy	2 (4%)
Salpingectomy	1 (2%)

Patients frequently underwent more than one surgical procedure during the same operation; therefore, percentages do not sum to 100%.

The surgical objective was complete excision of all visible endometriotic lesions whenever technically feasible. However, residual endometriotic disease was identified postoperatively in 3 of the 50 patients (6.0%), indicating that complete surgical excision could not be achieved in all cases. This finding is presented descriptively, and no inference regarding its association with postoperative health-related quality of life is made.

3.2. Changes in Health-Related Quality of Life from Preoperative to Six-Month Postoperative Assessment

HRQoL was assessed using the Short Form-36 (SF-36v2) questionnaire before surgery and at six-month follow-up (Table 4). Statistically significant improvements were observed across all eight domains (all $p < 0.001$, Wilcoxon signed-rank test). Large standardized effect sizes were observed for all domains (r = 0.74–0.87). Median improvements ranged from 16 to 50 points across individual SF-36 domains. All comparisons remained statistically significant after Holm–Bonferroni correction for multiple comparisons (Table 4). The largest median postoperative changes were observed for Role Limitations due to Physical Health and Bodily Pain (Table 5). The distribution of individual changes SF-36v2.domain scores between baseline and six-month follow-up is illustrated in Figure 2. Information on data availability and the number of complete paired observations for individual SF-36 domains and NRS pain intensity is provided in Supplementary Table S1.

Table 4. Comparison of preoperative and six-month postoperative SF-36v2 scores.

SF-36v2.Domain	Preoperative Median (IQR)	6-Month Postoperative Median (IQR)	Non-Zero Pairs, N	Z	*p*	Holm-Adjusted *p*	Effect Size (r)
Physical functioning	75 (60–90)	95 (90–100)	43	5.57	<0.001	<0.001	0.85
Role limitations due to physical health	0 (0–50)	75 (25–100)	43	4.96	<0.001	<0.001	0.76
Role limitations due to emotional problems	0 (0–33)	67 (33–100)	34	4.30	<0.001	<0.001	0.74
Vitality	30 (20–40)	50 (30–80)	46	5.20	<0.001	<0.001	0.77
Mental health	52 (36–64)	72 (52–88)	43	5.36	<0.001	<0.001	0.82
Social functioning	50 (38–75)	75 (63–100)	46	5.68	<0.001	<0.001	0.84
Bodily pain	35 (23–45)	78 (65–90)	45	5.81	<0.001	<0.001	0.87
General health	45 (35–60)	70 (55–80)	44	5.27	<0.001	<0.001	0.79

Abbreviations: IQR, interquartile range; Z, Wilcoxon signed-rank statistic; r, effect size. N indicates the number of non-zero paired observations included in the Wilcoxon signed-rank test; zero differences were excluded from the test statistic.

Table 5. Bootstrap 95% confidence intervals for median changes in SF-36 domain scores and NRS pain intensity.

Outcome	N	Median Δ	95% Bootstrap CI
Δ Physical Functioning	50	20	15–25
Δ Role Limitations due to Physical Health	50	50	25–75
Δ Role Limitations due to Emotional Problems	50	33	0–50.5
Δ Vitality	50	20	10–30
Δ Mental Health	50	16	14–26
Δ Social Functioning	50	25	13–25
Δ Bodily Pain	50	35	25–45
Δ General Health	49	20	10–25
Δ NRS	49	5	5–6

Abbreviations: Δ, median change between preoperative and postoperative assessment; CI, confidence interval; NRS, Numerical Rating Scale. Differences in N between the Wilcoxon and bootstrap analyses reflect the exclusion of zero differences from the Wilcoxon test statistic; bootstrap estimates were based on all available complete preoperative–postoperative pairs.

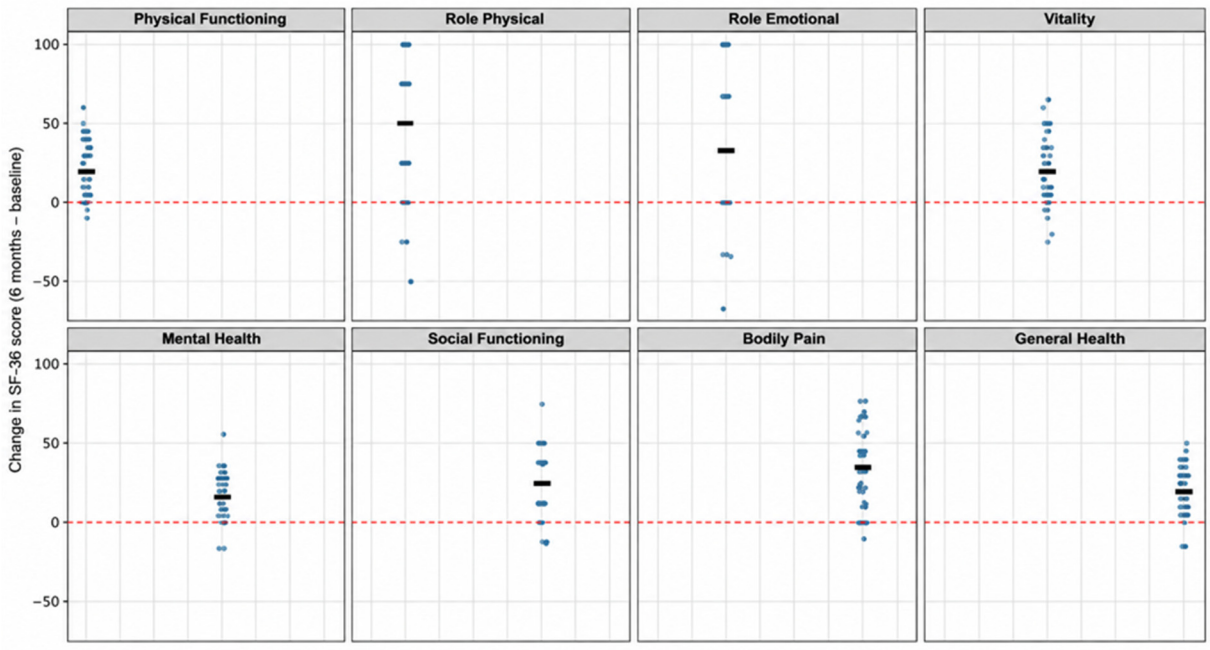


Figure 2. Individual changes in SF-36v2 domain scores from baseline to six-month follow-up. Each point represents an individual participant's change score (six-month minus baseline score). Positive values indicate improvement. Black horizontal markers indicate median changes, while red dashed lines indicate no change. SF-36, 36-Item Short Form Health Survey.

3.3. Changes in Pain Intensity

Pain intensity, assessed using the Numerical Rating Scale (NRS), decreased significantly following treatment (Table 6). The median NRS score declined from 8 (IQR: 7–8) preoperatively to 2 (IQR: 1–3) at the six-month postoperative assessment. The Wilcoxon signed-rank test demonstrated a highly significant reduction in pain intensity ($Z = 6.09$, $p < 0.001$), with a large effect size ($r = 0.87$). The reduction in pain intensity is illustrated in Figure 3.

Table 6. Comparison of preoperative and six-month postoperative NRS pain scores.

Outcome	Preoperative Median (IQR)	6-Month Postoperative Median (IQR)	Non-Zero Pairs, N	Z	*p*	Holm-Adjusted *p*	Effect Size (r)
NRS pain score	8 (7–8)	2 (1–3)	49	6.09	<0.001	<0.001	0.87

Abbreviations: IQR, interquartile range; Z, Wilcoxon signed-rank statistic; r, effect size; NRS, Numerical Rating Scale.

Additional longitudinal analyses using linear mixed-effects models adjusted for age and rASRM stage are presented in Supplementary Table S9. In the adjusted linear mixed-effects analyses, significant improvements were observed across all eight SF-36v2 domains and in NRS pain intensity (all $p < 0.001$). The adjusted improvement in Physical Functioning was 20.90 points (95% CI: 16.17–25.63), while the adjusted reduction in NRS pain intensity was 5.29 points (95% CI: 4.78–5.79). Full results are presented in Supplementary Table S6. These models accounted for repeated observations within participants and provided adjusted estimates of changes in SF-36v2 domains and NRS pain intensity between baseline and the six-month follow-up.

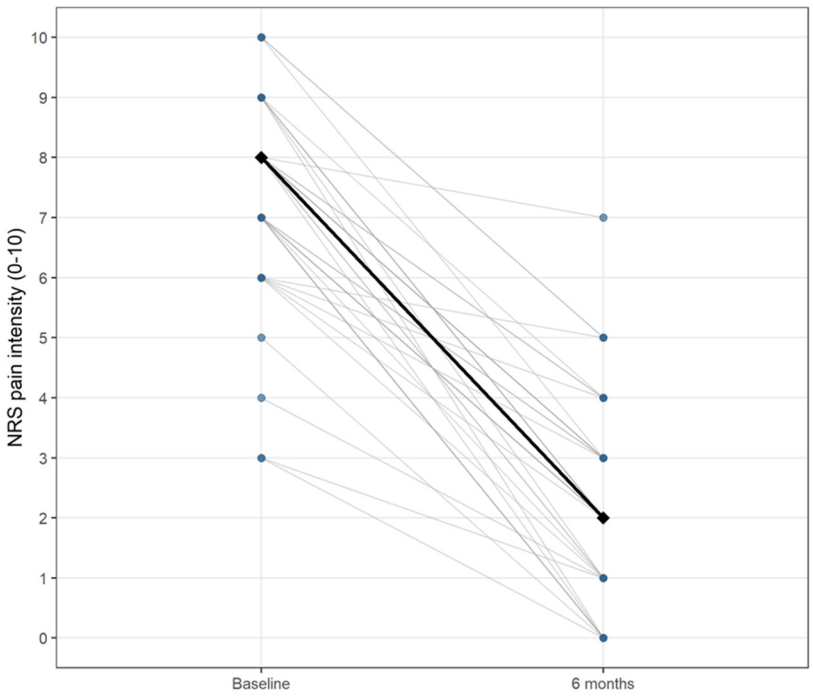


Figure 3. Paired NRS pain intensity scores at baseline and six-month follow-up. Grey lines connect individual paired observations. Blue points indicate observed NRS scores, and black diamonds connected by a solid line represent group medians. Lower NRS scores indicate less severe pain. NRS, Numeric Rating Scale.

3.4. Adjustment for Multiple Comparisons

To account for multiple hypothesis testing across the eight SF-36 domains, Holm–Bonferroni correction was applied. All comparisons remained statistically significant after Holm–Bonferroni correction for multiple comparisons (Table 4).

3.5. Association Between Pain Reduction and Improvement in Health-Related Quality of Life

Spearman rank correlation analysis evaluated the association between pain reduction (ΔNRS = preoperative minus postoperative NRS) and improvement in SF-36v2.domain

scores (ΔSF-36 = postoperative minus preoperative score) (Table 7). Positive weak-to-moderate correlations were observed across all SF-36 domains (ϱ = 0.274–0.538). Seven of eight correlations had unadjusted *p*-values below 0.05; after Holm–Bonferroni correction for the eight correlation tests, four associations remained statistically significant. Physical Functioning showed a positive but non-significant association (ϱ = 0.274, $p = 0.052$; Holm-adjusted $p = 0.064$). The strongest correlation was observed for Bodily Pain (ϱ = 0.538, Holm-adjusted $p < 0.001$), followed by Role Limitations due to Physical Health (ϱ = 0.478, Holm-adjusted $p = 0.004$), Vitality (ϱ = 0.459, Holm-adjusted $p = 0.006$), and Social Functioning (ϱ = 0.454, Holm-adjusted $p = 0.011$). These findings indicate that pain reduction was weakly to moderately associated with postoperative HRQoL improvement across individual domains. The relationship between changes in pain intensity and changes in the Bodily Pain domain is illustrated in Figure 4.

Table 7. Spearman correlations between reduction in pain intensity (ΔNRS) and changes in SF-36v2 domain scores (ΔSF-36).

SF-36 Domain	N	Spearman's ρ	*p*	Holm-Adjusted *p*
Physical functioning	49	0.274	0.052	0.064
Role limitations due to physical health	49	0.478	<0.001	0.004
Role limitations due to emotional problems	49	0.360	0.013	0.052
Vitality	49	0.459	0.001	0.006
Mental health	49	0.325	0.032	0.064
Social functioning	49	0.454	0.002	0.011
Bodily pain	49	0.538	<0.001	<0.001
General health	48	0.368	0.015	0.052

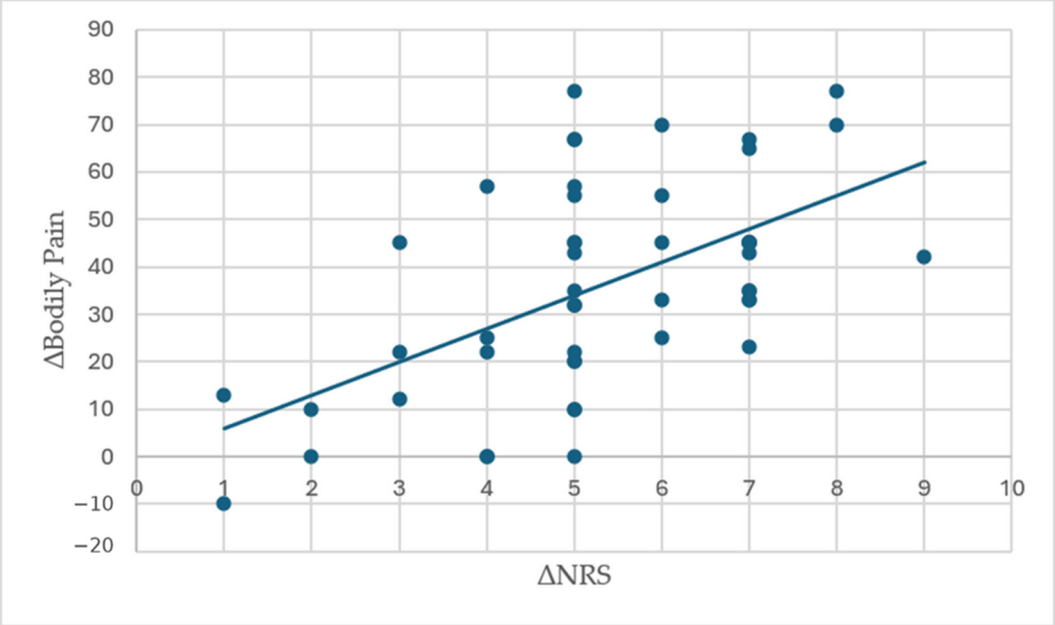


Figure 4. Scatter plot showing the relationship between changes in pain intensity (ΔNRS) and changes in the Bodily Pain domain of the SF-36v2 questionnaire. A moderate positive correlation was observed (Spearman's ϱ = 0.54). The regression line is shown for visualization only.

3.6. Comparison According to Disease Stage

Changes in pain intensity (ΔNRS) and SF-36v2 domain scores were compared between women with stage III and stage IV endometriosis (Supplementary Table S8). No statistically significant differences were detected between disease stages for pain reduction (ΔNRS: U = 190.0, $p = 0.44$) or for changes in any SF-36 domain (all $p > 0.05$). These

findings indicate that this cohort did not provide evidence of stage-related differences in postoperative change; they should not be interpreted as demonstrating equivalence between stage III and stage IV disease. The distribution of ΔNRS values according to disease stage is presented in Figure 5.

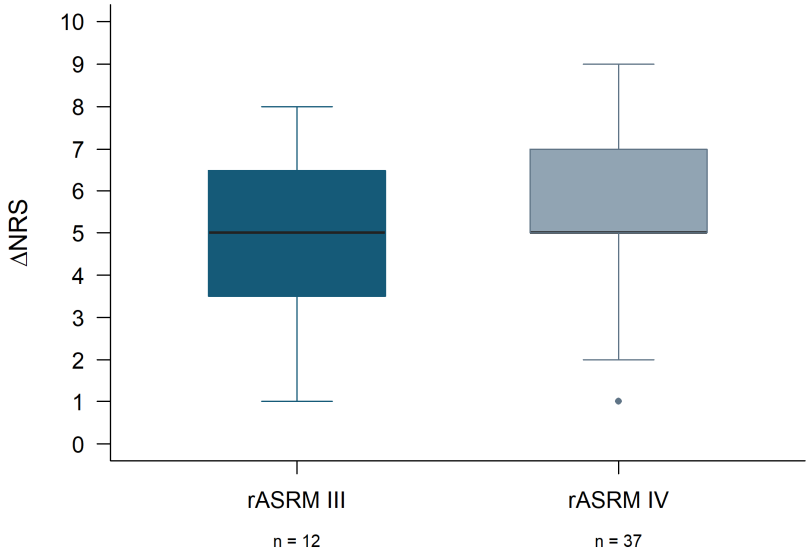


Figure 5. Comparison of changes in pain intensity (ΔNRS) between patients with stage III and stage IV endometriosis according to the rASRM classification. Box plots illustrate the distribution of ΔNRS values in both groups. No statistically significant difference in pain reduction was observed between disease stages (Mann–Whitney U test, $U = 190.0$, $p = 0.44$).

3.7. Comparison According to Postoperative Hormonal Treatment

Patients were classified into four postoperative hormonal treatment groups: dienogest (n = 19, 38%), GnRH-agonist (n = 16, 32%), combined EE/DNG (n = 11, 22%), and other hormonal treatment (n = 4, 8%). Postoperative hormonal treatment data were available for all 50 participants. All participants received postoperative hormonal treatment; none elected to attempt conception immediately after surgery without postoperative hormonal suppression. The Other group comprised three patients who received GnRH-antagonist with add-back treatment (relugolix/estradiol/norethisterone acetate; Ryeqo) and one patient who received medroxyprogesterone acetate. Due to the small size and pharmacological heterogeneity of this subgroup (n = 4), these patients were excluded from subsequent three-group exploratory comparisons. Treatment stability during the six-month follow-up in the three principal hormonal treatment groups is summarized in Supplementary Table S4. No treatment switching, temporary interruption, or permanent discontinuation occurred in these groups during the study observation period.

Baseline demographic and clinical characteristics of the three principal hormonal treatment groups are presented in Supplementary Table S2. These descriptive data were examined to assess potential baseline imbalance between the non-randomized treatment groups and should be considered when interpreting the exploratory comparisons of postoperative changes.

Comparison of change scores using the Kruskal–Wallis test (Table 8) showed no statistically significant differences among the three treatment groups in pain reduction (ΔNRS: $H(2) = 0.67$, $p = 0.72$) or in changes in any SF-36v2 domain (all $p > 0.05$). These findings provide no evidence of a difference in this small exploratory cohort; however, they should not be interpreted as demonstrating comparable treatment efficacy or therapeutic equivalence. Therefore, post hoc pairwise comparisons were not performed. Exploratory comparisons of changes in pain intensity and SF-36v2 domain scores across the

three principal hormonal treatment groups are presented in Table 7, with additional estimates and bootstrap confidence intervals provided in Supplementary Table S5. Baseline-adjusted ANCOVA analyses of six-month outcomes did not detect statistically significant overall treatment-group effects (Supplementary Table S3).

Table 8. Comparison of treatment outcomes according to postoperative hormonal treatment (Kruskal–Wallis test).

Outcome	H(2)	N	*p*	Holm-Adjusted *p*
Δ NRS	0.67	45	0.72	1.00
Δ Physical Functioning	4.04	46	0.13	1.00
Δ Role Limitations due to Physical Health	0.35	46	0.84	1.00
Δ Role Limitations due to Emotional Problems	1.55	46	0.46	1.00
Δ Vitality	0.25	46	0.88	1.00
Δ Mental Health	0.30	46	0.86	1.00
Δ Social Functioning	0.04	46	0.98	1.00
Δ Bodily Pain	1.47	46	0.48	1.00
Δ General Health	0.66	45	0.72	1.00

Abbreviations: Δ, change between preoperative and postoperative assessment; H(2), Kruskal–Wallis test with two degrees of freedom. N indicates the number of participants with available data for the respective outcome. Holm-adjusted *p*-values were calculated using the Holm–Bonferroni method to account for multiple comparisons.

3.8. Magnitude of Observed Postoperative Change

To quantify the magnitude and precision of within-participant changes, bootstrap 95% confidence intervals were calculated for median change scores in the overall cohort (Table 5). This analysis included participants receiving regimens categorized as other when outcome data were available. Median improvement ranged from 16 to 50 points across SF-36 domains. The largest median changes were observed for Role Limitations due to Physical Health (Δ = 50; 95% CI: 25–75) and Bodily Pain (Δ = 35; 95% CI: 25–45). Median pain reduction was 5 NRS points (95% CI: 5–6). These estimates describe the magnitude of observed change and should not, in the absence of a control group, be interpreted as causal treatment effects.

3.9. Adverse Effects According to Postoperative Hormonal Treatment

In our study, adverse effects were actively elicited from patients during follow-up visits. They were not assessed using a standardized adverse-event questionnaire. Adverse effects were assessed among patients receiving dienogest, GnRH-agonist, or combined EE/DNG therapy (Table 9). Spotting was reported in 36.8% of patients receiving dienogest, 31.3% of those receiving GnRH-agonist, and 27.3% of those receiving EE/DNG therapy.

Table 9. Comparison of adverse effects according to postoperative hormonal treatment.

Adverse Effect	Dienogest (n = 19)	GnRH-Agonist Therapy (n = 16)	Combined (n = 11)	*p*	Holm-Adjusted *p*
Spotting	7 (36.8%)	5 (31.3%)	3 (27.3%)	0.924	1.000
Mood disturbances	5 (26.3%)	4 (25.0%)	1 (9.1%)	0.658	1.000
Vaginal dryness	1 (5.3%)	6 (37.5%)	0 (0%)	0.011	0.089
Mastalgia	0 (0%)	0 (0%)	1 (9.1%)	0.239	1.000
Hot flushes	1 (5.3%)	9 (56.3%)	1 (9.1%)	0.001	0.010
Decreased libido	1 (5.3%)	3 (18.8%)	0 (0%)	0.273	1.000
Weight gain	0 (0%)	1 (6.3%)	0 (0%)	0.587	1.000
Oedema	1 (5.3%)	0 (0%)	0 (0%)	1.000	1.000
Headache	1 (5.3%)	0 (0%)	0 (0%)	1.000	1.000

Abbreviations: GnRH, gonadotropin-releasing hormone.

Hypoestrogenic symptoms were numerically more frequent in the GnRH-agonist group. Vaginal dryness was reported in 37.5% of patients in the GnRH-agonist group, compared with 5.3% in the dienogest group and 0% in the EE/DNG group. The overall distribution of hot flushes differed across the three hormonal treatment groups (Fisher–Freeman–Halton exact test, Holm-adjusted $p = 0.010$). Hot flushes were numerically most frequent in the GnRH-agonist group (56.3%), compared with the dienogest (5.3%) and EE/DNG (9.1%) groups. Because the global comparison for hot flushes remained statistically significant after Holm adjustment, exploratory pairwise Fisher exact tests were performed. Hot flushes were more frequent in the GnRH-agonist group than in the dienogest group (raw $p = 0.0017$; Holm-adjusted $p = 0.0052$) and the combined EE/DNG group (raw $p = 0.0183$; Holm-adjusted $p = 0.0366$), whereas no difference was observed between dienogest and EE/DNG (raw $p = 1.000$; Holm-adjusted $p = 1.000$), (Supplementary Table S7).

Decreased libido was reported in 5.3% of patients receiving dienogest, 18.8% of those receiving GnRH-agonist therapy, and none of those receiving EE/DNG therapy. Mastalgia, weight gain, oedema, and headache were uncommon, and no other adverse-effect comparison remained statistically significant after Holm adjustment.

Additional estimates, including confidence intervals for adverse-effect proportions and between-group differences, are provided in Supplementary Table S6.

4. Discussion

The observed postoperative improvements are consistent with previous studies and systematic reviews reporting favorable changes in quality of life after surgical treatment of endometriosis [6,7,9,12–14,23,26]. Earlier studies using generic and disease-specific patient-reported outcome measures have demonstrated improvements in physical functioning, pain, emotional well-being, and social functioning after surgery [6,7,9,13,14,23,26]. Current ESHRE guidelines recognize surgery as one of the therapeutic options for reducing endometriosis-associated pain and emphasize individualized decision-making based on symptoms, patient preferences, reproductive plans, potential adverse effects, and expected benefits [1].

Nevertheless, the magnitude of postoperative improvement observed in the present study should not be interpreted as a causal effect of surgery alone. All participants underwent surgical treatment followed by postoperative management, and the study did not include a non-surgical control group. Consequently, the observed within-participant changes may reflect the combined effects of surgery, postoperative hormonal treatment, recovery from the procedure, changes in pain perception over time, and other unmeasured factors. The present results therefore describe postoperative trajectories rather than isolate the independent therapeutic effect of surgery.

An important finding was the association between pain reduction and improvement in HRQoL. The strongest correlation was observed for the Bodily Pain domain, whereas associations with the remaining SF-36v2.domains were weak to moderate. Physical Functioning showed a positive but non-significant association. This pattern suggests that pain relief is associated with postoperative recovery, while changes in broader aspects of quality of life may also reflect factors not captured by pain intensity alone. HRQoL in women with endometriosis is multidimensional and may also be influenced by fatigue, emotional well-being, infertility-related concerns, sexual function, social participation, work productivity, treatment burden, and expectations regarding recovery [4,20,27].

The lack of a strong relationship between pain reduction and every dimension of HRQoL is clinically relevant. A patient may experience substantial improvement in pelvic pain while continuing to report limitations related to emotional health, fatigue, fertility

concerns, or social functioning. Conversely, improvement in psychological well-being and daily functioning may occur even when residual pain persists. These observations support the inclusion of multidimensional patient-reported outcomes alongside conventional pain measures when evaluating treatment outcomes in endometriosis.

No statistically significant differences in postoperative changes in NRS pain or SF-36 scores were detected between women with rASRM stage III and stage IV disease. However, these findings should not be interpreted as demonstrating equivalent postoperative outcomes between disease stages. The relatively small number of women with stage III disease limited statistical power, and the rASRM classification primarily describes anatomical disease extent rather than the full clinical burden of endometriosis. Previous research has also demonstrated an imperfect relationship between anatomical disease severity, pain intensity, and patient-reported quality of life [20]. Thus, anatomical stage alone may be insufficient to predict the magnitude of postoperative improvement.

The generalisability of the findings should be considered in the context of the study population and setting. This was a single-center study conducted in a specialized gynecological department and included women with surgically confirmed stage III–IV endometriosis. Therefore, the findings may be most applicable to patients with advanced endometriosis treated in similar specialized or tertiary-care settings and should not be directly generalised to all women with endometriosis, including those with less advanced disease or those treated in different healthcare settings.

4.1. Postoperative Hormonal Treatment

Postoperative hormonal treatment represents an important component of endometriosis management in women who do not intend to conceive immediately after surgery. Current ESHRE recommendations indicate that postoperative hormonal therapy may be offered to women not seeking immediate pregnancy and emphasize shared decision-making that takes into account individual efficacy, adverse effects, preferences, costs, availability, and reproductive plans [1].

In the present cohort, exploratory comparisons did not detect statistically significant differences in pain reduction or improvement in any SF-36v2 domain among women initially assigned to dienogest, GnRH-agonist, or combined EE/DNG treatment. These findings require cautious interpretation. Treatment allocation was not randomized, subgroup sizes were small, and the analyses were not powered to demonstrate equivalence or non-inferiority. Accordingly, failure to detect a statistically significant between-group difference cannot be interpreted as evidence that the three regimens have comparable efficacy.

Baseline characteristics of the hormonal treatment groups are particularly relevant to the interpretation of these exploratory comparisons. Postoperative therapy was selected according to clinical considerations, contraindications, reproductive plans, and patient preference rather than randomized allocation. Consequently, baseline differences may have influenced both treatment selection and subsequent outcomes, creating the possibility of selection bias and confounding by indication. Descriptive baseline characteristics according to hormonal regimen are therefore provided in Supplementary Table S1 to allow assessment of potential baseline imbalance. These include age, BMI, rASRM stage, infertility history, baseline NRS pain intensity, and baseline scores across all eight SF-36v2 domains.

This consideration is especially important when comparing change scores. Participants beginning treatment with greater pain intensity or poorer baseline HRQoL may have had greater potential for numerical improvement than participants with less severe baseline impairment. Therefore, unadjusted comparisons of ΔNRS and ΔSF-36 should be regarded as descriptive and hypothesis-generating rather than as estimates of comparative treatment effectiveness.

The absence of statistically significant differences in the present study should also be considered in the context of the existing literature. Dienogest, EE/DNG, GnRH agonists, and GnRH antagonists are established hormonal approaches for reducing endometriosis-associated pain, although their mechanisms, indications, and tolerability profiles differ [1,10,15,16,21,22,28–30]. Comparative evidence for dienogest and GnRH-agonist treatment has not established clear superiority of one strategy for pain outcomes and indicates clinically relevant differences in adverse-effect profiles [11,22,28,30]. Importantly, such external evidence should not be used to infer equivalence within the present cohort.

4.2. Adverse Effects and Tolerability

Differences in treatment tolerability may be particularly relevant when postoperative hormonal treatment is continued for several months or longer. In the present study, the overall distribution of hot flushes differed significantly across the three principal hormonal treatment groups after adjustment for multiple comparisons. Hot flushes were numerically most frequent in the GnRH-agonist group. Exploratory pairwise post hoc Fisher exact tests showed that hot flushes were more frequent in the GnRH-agonist group than in the dienogest group (56.3% vs. 5.3%; raw $p = 0.0017$, Holm-adjusted $p = 0.0052$) and the combined group (56.3% vs. 9.1%; raw $p = 0.0183$, Holm-adjusted $p = 0.0366$). No significant difference was observed between the dienogest and combined groups (5.3% vs. 9.1%; raw $p = 1.000$, Holm-adjusted $p = 1.000$).

The observed pattern is biologically plausible and broadly consistent with the known pharmacological effects of GnRH suppression. GnRH agonists produce marked suppression of ovarian estrogen production and are therefore associated with hypoestrogenic adverse effects, including hot flushes, vaginal dryness, reduced libido, and potential loss of bone mineral density [22]. Contemporary evidence comparing postoperative dienogest with GnRH agonists similarly suggests that vaginal bleeding is more frequent with dienogest, whereas hot flushes are more frequently associated with GnRH agonist treatment [22].

Interpretation of the GnRH-agonist group nevertheless requires caution. This group consisted of patients receiving triptorelin without add-back therapy. The separate Other group included three patients receiving Ryeqo, an oral GnRH-antagonist-based combination with built-in add-back therapy, and one patient receiving medroxyprogesterone acetate. These regimens were not included in the three-group comparisons because of their small numbers and pharmacological heterogeneity.

Adverse-effect assessment also differed from a formal safety evaluation used in randomized clinical trials. Symptoms were collected during follow-up without a standardized adverse-event questionnaire or predefined symptom checklist, and individual participants could report more than one symptom. No treatment switching, temporary interruption, or permanent discontinuation occurred during the six-month observation period. Some treatment modifications were made after the final six-month assessment because of tolerability concerns; however, these subsequent changes were outside the predefined study period and were not included in the analyses. The absence of a standardized adverse-event questionnaire remains a limitation when interpreting differences in adverse-effect frequencies.

From a patient-centered perspective, tolerability remains important because adverse effects may themselves influence HRQoL and adherence. Irregular bleeding, vasomotor symptoms, vaginal dryness, mood changes, and reduced libido may affect physical, emotional, sexual, and social well-being. Current guidelines therefore emphasize that selection of hormonal therapy should incorporate patient preferences and adverse-effect profiles rather than relying exclusively on expected effects on pain [1].

4.3. Strengths and Limitations

The strengths of this study include its prospective design, paired preoperative and six-month postoperative assessment of pain and multidimensional HRQoL, reporting of effect sizes and bootstrap confidence intervals, and evaluation of associations between pain reduction and individual SF-36 domains. The study also provides exploratory data on postoperative hormonal treatment and patient-reported adverse effects in women with advanced endometriosis.

Several limitations should be acknowledged. First, this was a single-center observational cohort without a non-surgical control group, precluding causal attribution of the observed improvements to surgery alone. The modest sample size, particularly within hormonal treatment subgroups, limited statistical power for between-group comparisons. Moreover, postoperative hormonal treatment was not randomized, and potential baseline imbalance, selection bias, and confounding by indication cannot be excluded. Supplementary Table S2 provides descriptive baseline characteristics of the principal treatment groups. The small and heterogeneous Other group was excluded from the exploratory three-group comparisons. Although treatment regimens remained unchanged during the six-month observation period, treatment persistence beyond six months was not systematically evaluated.

Second, adverse effects were collected without a standardized questionnaire or predefined checklist and should therefore be interpreted descriptively. The small treatment groups also limited the assessment of less frequent adverse effects, and pairwise comparisons for hot flushes should be considered exploratory. Third, follow-up was limited to six months, preventing assessment of long-term symptom recurrence, durability of HRQoL improvement, reproductive outcomes, and long-term treatment tolerability. Finally, although the SF-36 is a validated generic HRQoL instrument, it does not fully capture endometriosis-specific concerns such as infertility-related distress, dyspareunia, sexual functioning, treatment burden, or concerns about recurrence. Future studies should consider combining generic and disease-specific instruments such as the EHP-30.

Preoperative medical treatment was documented in 14 participants (28.0%). However, information on treatment type, duration, and response was incomplete, preventing a reliable assessment of its potential influence on postoperative outcomes. This represents an additional source of heterogeneity and residual confounding.

Overall, substantial improvements in pain and multiple dimensions of HRQoL were observed during the six months following surgery and postoperative management. Pain reduction was associated with HRQoL improvement, although this relationship varied across domains. Exploratory analyses did not identify statistically significant differences in improvement among the principal hormonal treatment groups; however, the non-randomized design and small subgroup sizes preclude conclusions regarding comparative efficacy or equivalence. Larger multicenter studies with longer follow-up and appropriately designed comparative analyses are needed to clarify the effectiveness and tolerability of postoperative hormonal strategies.

5. Conclusions

Six months after surgery and subsequent hormonal treatment for advanced endometriosis, women in this cohort showed substantial improvements across all SF-36v2 domains and a marked reduction in pain. Weak-to-moderate associations between pain reduction and HRQoL improvement indicate that changes in HRQoL were only partly associated with changes in pain. Because all participants underwent surgery and postoperative management without a non-surgical control group, these within-participant changes should not be interpreted as causal effects of surgery alone.

Exploratory analyses did not detect statistically significant differences in pain or HRQoL improvement among the three principal postoperative hormonal treatment groups. Because treatment allocation was non-randomized, subgroup sizes were small, and baseline imbalance and confounding by indication cannot be excluded, these findings do not establish comparative efficacy or treatment equivalence. The overall distribution of hot flushes differed significantly across hormonal treatment groups, with exploratory pairwise analyses indicating higher frequency in the GnRH-agonist group compared with both the dienogest and EE/DNG groups.

Larger multicentre studies with longer follow-up and disease-specific patient-reported outcomes are needed to clarify predictors of postoperative recovery and the comparative effectiveness and tolerability of postoperative hormonal strategies.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm15228872/s1, Table S1. Baseline and six-month follow-up assessments (total study population: N = 50); Table S2. Baseline characteristics of the three principal postoperative hormonal treatment groups; Table S3. Baseline-adjusted comparisons of six-month postoperative outcomes between hormonal treatment groups (ANCOVA); Table S4. Hormonal treatment stability during the six-month study follow-up; Table S5. Comparison of treatment outcomes according to postoperative hormonal treatment (Kruskal–Wallis test); Table S6. Comparison of adverse effects according to postoperative hormonal treatment; Table S7. Post-hoc pairwise comparisons of hot flushes between postoperative hormonal treatment groups (Fisher's exact test with Holm adjustment); Table S8. Comparison of changes in NRS pain intensity and SF-36 domain scores between patients with stage III and stage IV endometriosis (Mann–Whitney U test); Table S9 Multivariable repeated-measures analysis of changes in SF-36 domains and NRS pain intensity; Figure S1. Distribution of changes in SF-36 domain scores by postoperative hormonal treatment group. Boxplots show changes from baseline to six months after surgery, calculated as postoperative minus preoperative scores.

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