Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Effectiveness and safety of dydrogesterone versus dienogest after laparoscopic cystectomy for ovarian endometrioma: a multicenter prospective cohort study

Jiao Liu
Guangdong Province Women and Children Hospital
Wenjing Lu
Guangdong Province Women and Children Hospital
Huazhang Miao
Guangdong Province Women and Children Hospital
Xiaowan Luo
Zhongshan Bo'ai Hospital
Xinke Zhao
Longgang Central Hospital of Shenzhen
Mingshan Zhu
The First People ' s Hospital of Foshan
Li Li
lili-1406@163.com

Guangdong Province Women and Children Hospital

Research Article

Keywords: ovarian endometrioma, dydrogesterone, dienogest, postoperative treatment, VAS pain score

Posted Date: November 12th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11504446/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Title page

Article title

Effectiveness and safety of dydrogesterone versus dienogest after laparoscopic cystectomy for ovarian endometrioma: a multicenter prospective cohort study

Authors

Jiao Liu[a,b,†], Wenjing Lu[a,†], Huazhang Miao, PhD[a,†], Xiaowan Luo[c], Xinke Zhao[d], Mingshan Zhu[e], Li Li, MD[a,*]

Affiliations

[a] Institute of Women and Children's Health, Guangdong Women and Children Hospital (Women and Children's Hospital, Southern University of Science and Technology), Guangzhou 511442, Guangdong, P.R. China.

[b] Graduate School, Guangzhou Medical University, Guangzhou 511436, Guangdong, P.R. China.

[c] Department of Gynecology, Zhongshan Bo'ai Hospital, Zhongshan528403, Guangdong, P.R. China.

[d] Department of Gynecology, Longgang Central Hospital of Shenzhen, Shenzhen 518116, Guangdong, P.R. China.

[e] Department of Gynecology, The First People's Hospital of Foshan, Foshan 528000, Guangdong, P.R. China.

[†] Jiao Liu, Wenjing Lu, and Huazhang Miao contributed equally to this work and share first authorship.

Corresponding author

*Li Li, MD, PhD, Prof.

Institute of Women and Children's Health, Guangdong Women and Children Hospital

No. 521 Xingnan Avenue, Panyu District

Guangzhou 511442, Guangdong, P.R. China

Tel: +86-020-39151961; +86-13631446859

Email: lili-1406@163.com

Article type

Research, Prospective Multicenter Cohort Study

Word counts and manuscript components

Main text word count: 2995

Abstract word count: 334

References: 29

Main text: 3 tables and 4 figures

Supplementary material: 4 supplementary tables and 3 supplementary figures and 1 appendices

Abstract

Background: Prospective evidence to guide the choice between dydrogesterone and dienogest after laparoscopic cystectomy for ovarian endometrioma remains limited. This study compared their effectiveness and safety in women of reproductive age to inform individualized postoperative treatment.

Methods: This prospective multicenter cohort enrolled women aged 18–45 years who underwent laparoscopic cystectomy for histologically confirmed ovarian endometrioma at four hospitals in Guangdong Province, China. Patients and clinicians jointly selected postoperative therapy with either dydrogesterone (10 mg twice daily on cycle days 5–25) or continuous dienogest (2 mg daily) during routine care. The primary outcome was the change in visual analog scale (VAS) pain score from preoperative baseline to week 24. Between-group differences were estimated using covariate-adjusted analysis of covariance with HC3 robust standard errors. The study was registered at ClinicalTrials.gov (NCT05976529) on 25 April 2023.

Results: A total of 242 women were enrolled: 109 initiated dydrogesterone and 133 initiated dienogest; 234 (96.7%) had VAS data available at week 24. The adjusted between-group difference in VAS pain score change was 0.00 points (95% CI, −0.44 to 0.43; P = 0.983; dydrogesterone minus dienogest), and estimates were similar across sensitivity analyses. At week 24, the improvement in the Mental Component Summary score of the 12-Item Short Form Health Survey was greater with dydrogesterone (adjusted mean difference, 5.32 points; 95% CI, 2.28 to 8.35; Benjamini-Hochberg [BH]-adjusted P = 0.004). Cyclic bleeding was the predominant

bleeding pattern in the dydrogesterone group, whereas no bleeding was the predominant pattern in the dienogest group. Through week 24, any adverse event was reported in 38.1% of the dydrogesterone group versus 54.3% of the dienogest group (BH-adjusted P = 0.063); anxiety or depression (5.7% vs 22.5%; BH-adjusted P = 0.009) and insomnia (4.8% vs 17.8%; BH-adjusted P = 0.018) were reported less frequently with dydrogesterone than with dienogest.

Conclusions: After adjustment, the improvement in VAS pain score at 24 weeks did not differ significantly between dydrogesterone and dienogest. Differences in mental well-being, adverse events, and bleeding patterns may help guide individualized postoperative treatment decisions.

Keywords: ovarian endometrioma; dydrogesterone; dienogest; postoperative treatment; VAS pain score.

Background

Ovarian endometrioma is a common ovarian manifestation of endometriosis and is associated with pelvic pain, infertility, and diminished ovarian reserve[1]. Laparoscopic cystectomy can relieve symptoms when surgery is indicated, but may further compromise ovarian reserve[1-3]. Pain may persist and endometriomas may recur after surgery[4, 5]. Postoperative management should therefore aim to control symptoms and reduce recurrence risk while taking into account ovarian reserve and pregnancy plans[1, 2].

Progestogens are among the first-line hormonal options for postoperative

management after endometrioma cystectomy in women not seeking immediate pregnancy[2]. Commonly used oral progestogens include dienogest, norethisterone, and medroxyprogesterone acetate[6]. Dienogest is the most extensively studied oral progestogen for endometriosis, with evidence supporting pain relief and a reduced risk of postoperative endometrioma recurrence[7, 8]. However, bleeding disturbances and mood symptoms may affect tolerability[9]. Its suppression of ovulation also limits its use in women actively trying to conceive[10]. Studies of dydrogesterone have reported pain relief and stabilization or reduction of endometrioma volume[11, 12]. Luteal-phase dydrogesterone has also been studied for pain relief in women attempting conception[13]. However, prospective evidence to guide the choice between dydrogesterone and dienogest after endometrioma cystectomy remains limited, particularly regarding pain, quality of life, ovarian reserve, bleeding, adverse events, and treatment completion.

To inform individualized postoperative treatment for women of reproductive age, this multicenter prospective cohort study compared the efficacy and safety of postoperative dydrogesterone versus dienogest following laparoscopic cystectomy for ovarian endometrioma.

Methods

Design

This multicenter prospective cohort study was conducted at four hospitals in Guangdong Province, China: Guangdong Women and Children Hospital, The First People’s Hospital of Foshan, Zhongshan Bo’ai Hospital, and Longgang Central

Hospital of Shenzhen. Women aged 18 to 45 years who underwent laparoscopic cystectomy for histopathologically confirmed ovarian endometrioma were enrolled from May 17, 2023, through March 16, 2026. The data collection cutoff date was September 9, 2026.

Eligible women met at least one of the following indications for surgery: an ovarian cyst ⩾4 cm in diameter, infertility, or pain refractory to medical therapy. They had not received hormonal treatment for endometriosis during the 3 months before study treatment initiation and had no coexisting endocrine disorder. Women were excluded if they had known hypersensitivity to or a contraindication to the selected study medication, severe hepatic or renal dysfunction, or malignancy.

Treatment exposure was classified according to the initial postoperative regimen. Treatment began during the first menstrual cycle after surgery: dydrogesterone was administered at 10 mg twice daily on cycle days 5–25, and dienogest at 2 mg once daily continuously from cycle day 1. Regimen selection was made jointly by the treating physician and patient as part of routine clinical care, without randomisation. Follow-up assessments were conducted at 12 and 24 weeks after treatment initiation.

The study was registered with ClinicalTrials.gov (NCT05976529) and received ethics approval (GuangdongWCH[202301128]). All participants provided written informed consent before enrolment.

Measures

Investigators at all centers received standardized training and followed a common investigator manual, with regular quality-control checks to promote

consistency in data collection and outcome assessment.

Before surgery and at weeks 12 and 24, participants rated average pain across the most recent menstrual cycle on a 0 – 10 visual analog scale (VAS). At visits without menstrual bleeding, the most recent expected cycle was estimated from each woman's pretreatment menstrual pattern. Change in VAS score from baseline to week 24 was the primary outcome; the week-12 analysis was supportive.

Secondary outcomes included changes from the preoperative baseline in Cox Menstrual Symptom Scale (CMSS) scores and the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores of the 12-Item Short Form Health Survey(SF-12) at weeks 12 and 24, and in serum cancer antigen 125 (CA-125) and anti-Müllerian hormone (AMH) at week 24. CMSS severity and duration ratings (0 – 4 each) were summed across 18 symptoms to yield a total score of 0 – 144, with higher scores indicating greater symptom burden[14]. SF-12v2 composite scores were calculated using the 1998 US norm-based scoring algorithm, with higher scores indicating better health-related quality of life (Appendix A)[15].

Bleeding pattern, volume, and duration were recorded separately during weeks 0 – 12 and 13 – 24. Patterns were classified as cyclic, irregular, or absent. At each follow-up visit, clinicians asked about potential adverse effects of the prescribed medication and documented both elicited and spontaneous patient reports. Adverse events were summarized cumulatively through weeks 12 and 24, with each participant counted once per event category. Treatment completion was defined as completion of the initially prescribed 24-week regimen. The timing and reasons for drug switches,

transitions to luteal-phase dydrogesterone, and treatment discontinuation were recorded. Recurrence was defined as a newly detected endometrioma-compatible cyst greater than 2 cm in maximum diameter, confirmed on at least two ultrasound examinations during the 24-week follow-up[16]. Pregnancy was recorded among women who intended at baseline to conceive within 24 weeks; those who conceived were followed through delivery or pregnancy loss.

All women underwent ovarian-sparing laparoscopic cystectomy, with adhesiolysis and excision of visible endometriotic lesions, including deep infiltrating endometriosis (DIE). Disease extent was scored intraoperatively using the revised American Society for Reproductive Medicine (rASRM) classification[17]. Covariates were selected for their relevance to treatment selection or outcomes: study center, age, body mass index, rASRM score, ovarian cyst diameter, DIE, fertility intention, infertility, and parity.

Sample Size

Based on previous studies[12, 18],mean reductions in VAS score of 2.3 and 1.8 points were assumed for the dydrogesterone and dienogest groups, respectively, corresponding to a between-group difference of 0.5 points. Assuming a common standard deviation of 1.13 points, a two-sided α of 0.05, 80% power, equal allocation, and 20% attrition, the required sample size was 206 participants (103 per group).

Statistical analysis

Continuous variables were summarised as means (standard deviations) or

175 medians (interquartile ranges), and categorical variables as numbers (percentages).
176 Baseline balance was assessed using absolute standardised mean differences. Binary
177 and multicategory outcomes were compared using Fisher's exact and Fisher–
178 Freeman–Halton tests, respectively, with 100,000 Monte Carlo replicates for the
179 latter.

180 The primary 24-week between-group difference in VAS change was estimated
181 using analysis of covariance adjusted for baseline VAS and the prespecified
182 covariates. CMSS, PCS, and MCS scores were analysed similarly. HC3
183 heteroscedasticity-consistent standard errors were used, and adjusted mean
184 differences were calculated as dydrogesterone minus dienogest. CA-125 and AMH
185 were natural-log transformed and analysed using analogous baseline-adjusted models,
186 with effects reported as geometric mean ratios. Bleeding-duration outcomes were
187 analysed using covariate-adjusted linear models. Benjamini–Hochberg (BH)
188 adjustment was applied separately within the prespecified outcome families.

189 All analyses were based on the initial treatment group. Complete-case analyses
190 were primary. Sensitivity analyses included restriction to participants completing
191 treatment, propensity-score overlap weighting, exclusion of influential observations,
192 and multiple imputation. Missing VAS, CA-125, and AMH outcomes were imputed
193 by predictive mean matching in 50 datasets under missing-at-random and prespecified
194 missing-not-at-random scenarios; estimates were pooled using Rubin's rules. All tests
195 were two-sided, with $P<0.05$ considered statistically significant. Analyses were
196 performed using R version 4.4.1.

Results

Study population and baseline characteristics

Of 247 women assessed for eligibility after surgery, 5 were excluded and 242 enrolled: 109 initiated dydrogesterone and 133 initiated dienogest (Figure 1). Follow-up assessments were available for 238 women (98.3%) at week 12 and 234 (96.7%) at week 24, with similar timing between groups (Supplementary Table S1). The planned 24-week regimen was completed by 82/109 (75.2%) dydrogesterone recipients and 114/133 (85.7%) dienogest recipients (Supplementary Table S2).

Baseline characteristics differed between groups, particularly by study centre and reproductive characteristics (Table 1). Compared with dienogest recipients, dydrogesterone recipients more often reported infertility (21.1% vs 3.0%) or intended to conceive (39.4% vs 18.8%) and were less often parous (43.1% vs 66.9%). Dysmenorrhoea was reported by 231 women (95.5%; Supplementary Table S3).

Primary outcome

Observed mean VAS pain scores decreased from baseline at 12 and 24 weeks in both groups (Figure 2A). At week 24, the unadjusted between-group difference in VAS change (dydrogesterone minus dienogest) was 0.50 points (95% CI, −0.08 to 1.08), which decreased to 0.00 points (95% CI, −0.44 to 0.43; P = 0.983) after adjustment for baseline VAS and prespecified covariates. At week 12, the corresponding unadjusted and adjusted differences were 0.42 points (95% CI, −0.10 to 0.94) and 0.11 points (95% CI, −0.35 to 0.56; P = 0.647; Table 2). Sensitivity analyses of the 24-week VAS outcome were consistent with the primary analysis,

with estimates ranging from −0.14 to 0.10 points and all 95% CIs including zero (Supplementary Figure S1). Overlap weighting achieved adequate covariate balance, with all absolute standardised mean differences below 0.10 (Supplementary Figure S2).

Secondary outcomes

CMSS scores decreased and SF-12 PCS and MCS scores increased in both groups (Figure 2B – D). After BH adjustment, only the 24-week MCS change differed between groups, with a greater increase in the dydrogesterone group (adjusted mean difference, 5.32 points; 95% CI, 2.28 – 8.35; BH-adjusted P=0.004; Table 3). At week 24, CA-125 and AMH measurements were available for 176 and 187 women, respectively. Both markers declined from baseline in each group (Figure 2E,F); adjusted geometric mean ratios were 1.07 (95% CI, 0.90 – 1.27) and 1.02 (95% CI, 0.79 – 1.33), respectively (Table 3). Missing-data sensitivity analyses yielded similar estimates (Supplementary Figure S3).

Bleeding pattern and volume differed between regimens in both 12-week periods (all BH-adjusted P<0.001; Figure 3A–D). Cyclic bleeding predominated with dydrogesterone (83.7% and 87.8%), and normal-volume bleeding was the most common volume category. With dienogest, the proportion with no bleeding rose from 48.5% to 71.9%, while irregular bleeding fell from 43.9% to 21.1%. The longest bleeding or spotting episode and total bleeding or spotting days were greater with dydrogesterone in both periods (Figure 3E).

Any adverse event was reported in 31.1% versus 47.0% through week 12 and

38.1% versus 54.3% through week 24 with dydrogesterone versus dienogest; the BH-adjusted P value was 0.063 at both time points. Anxiety or depression was reported less often with dydrogesterone through weeks 12 and 24 (4.7% vs 18.9% and 5.7% vs 22.5%; BH-adjusted P=0.017 and 0.009, respectively), as was insomnia through week 24 (4.8% vs 17.8%; BH-adjusted P=0.018; Figure 4; Supplementary Table S4).

During the 24-week treatment period, 17 of the 68 women with baseline fertility intention attempted conception: 14 in the initial dydrogesterone group and 3 in the initial dienogest group. Among the 13 dydrogesterone recipients who transitioned to luteal-phase dosing, 8 subsequently conceived, of whom 6 had live births. The woman who did not transition to luteal-phase dosing also conceived and had a live birth. Two of the three women in the initial dienogest group conceived, and both had live births (Supplementary Table S2). Three additional women in the initial dydrogesterone group conceived in the first menstrual cycle after completing the planned 24-week regimen and stopping treatment; all three had live births. Ultrasonographic endometrioma recurrence by week 24 occurred in 3/105 (2.9%) and 3/129 (2.3%) women in the respective groups (P>0.99).

Discussion

The global total fertility rate declined from 4.84 births per woman in 1950 to 2.23 in 2021 and is projected to decline further[19]. Against this background, balancing symptom control and recurrence prevention with timely conception remains a key challenge in postoperative care for women with ovarian endometrioma who wish to

conceive. Treatment decisions should therefore consider effectiveness alongside tolerability, quality of life, and changing reproductive plans.

Efficacy and quality of life

Dienogest has established efficacy for endometriosis-associated pain and evidence supporting a reduction in postoperative endometrioma recurrence, making it a clinically relevant active comparator[7, 8]. In this multicenter prospective cohort, the adjusted between-group difference in VAS pain-score change at 24 weeks was close to zero, with consistent estimates across sensitivity analyses. A previous single-center retrospective study by the same research group, now in press, also reported broadly similar six-month VAS pain-score changes across four postoperative hormonal regimens, including dydrogesterone and dienogest. The present study extends this evidence through prospective assessment across four centers and a focused comparison of these two regimens after laparoscopic cystectomy. The absence of a clear between-group difference in pain relief does not establish equivalence. Because baseline pain was assessed before surgery, the observed improvements may reflect surgery and recovery as well as hormonal treatment.

Although CA-125 is nonspecific and cannot alone establish treatment response or recurrence[20], changes in its levels may help inform assessment when interpreted alongside clinical and imaging findings. Previous studies have reported CA-125 declines after endometrioma surgery and variable changes during dienogest or dydrogesterone treatment[12, 21, 22]. Differences in surgical status, disease characteristics, and follow-up may partly explain this variability. In the present cohort,

CA-125 levels at 24 weeks did not clearly differ between groups after adjustment for baseline CA-125 and other prespecified covariates, with similar findings after multiple imputation. Ultrasound detected three endometrioma recurrences in each group, with no clear between-group difference over 24 weeks. These findings raise the possibility that the two regimens offer similar short-term protection against endometrioma recurrence. Longer follow-up is needed to assess whether recurrence rates differ between the regimens over time.

Pain relief and ovarian endometrioma recurrence, however, capture only part of postoperative recovery. CMSS and SF-12 PCS scores improved in both groups without clear between-group differences, whereas SF-12 MCS scores improved more with dydrogesterone at 24 weeks. Previous single-agent cohorts reported improvements in dysmenorrhea and SF-20 scores with dydrogesterone[11], and in pain and all EHP-30 domains with dienogest[23]. Their different measures and lack of a direct comparison provide only indirect context for the present CMSS and SF-12 findings. These findings suggest that mental health-related quality of life may help inform postoperative treatment selection, even when pain and recurrence outcomes do not clearly differ between regimens.

Safety and tolerability

The adverse-event and bleeding findings further distinguish the treatment experience despite the absence of a clear difference in pain relief and ovarian endometrioma recurrence. Dydrogesterone was associated with fewer reports of anxiety or depression and insomnia than dienogest. Bleeding was predominantly

cyclic with dydrogesterone, whereas dienogest was associated with more irregular bleeding during the first 12 weeks and more frequent absence of bleeding by week 24. The greater total number of bleeding/spotting days with dydrogesterone may partly reflect continued cyclic bleeding and does not necessarily indicate a worse bleeding experience. Previous studies have linked treatment-related bleeding changes to disruption of daily life and treatment discontinuation, although preferences vary[24, 25]. The clinical importance of these patterns therefore depends partly on whether a woman prefers cyclic bleeding or the absence of bleeding. Whether bleeding contributed to the MCS, mood, or sleep findings remains uncertain because perceived bleeding predictability and its relationship with these outcomes were not assessed. Completion of the planned 24-week regimen was 75.2% with dydrogesterone and 85.7% with dienogest. Completion was not a direct measure of tolerability because noncompletion also reflected pregnancy planning, treatment changes, patient preference, and loss to follow-up.

Ovarian reserve and pregnancy planning

Reproductive planning adds two related considerations: ovarian reserve after surgery and the opportunity to attempt conception. AMH declined in both groups, but adjusted levels at 24 weeks did not clearly differ between groups, with similar findings after multiple imputation. These declines are consistent with reports that AMH may remain below preoperative levels for up to 18 months after cystectomy[3, 26]. Evidence that hormonal treatment modifies the postoperative AMH course remains limited. One study found similar three-month AMH reductions with

postoperative dienogest and no treatment[27], whereas a small perioperative randomized trial reported higher one-year AMH ratios with dienogest than with a GnRH agonist[28]. Without a surgery-only group, the present study could not determine whether either regimen altered the postoperative AMH course. Moreover, AMH poorly predicts spontaneous conception or live birth[29], so these findings cannot establish effects on fertility.

The cohort also illustrates how treatment may need to change when pregnancy becomes an immediate priority. Among 14 dydrogesterone recipients who attempted conception, 13 transitioned to a luteal-phase regimen, and eight of these 13 conceived. Two of three women attempting conception in the initial dienogest group also conceived. Luteal-phase dydrogesterone has previously been studied for pain control during attempts at conception[13]. Such a transition may offer a practical way to accommodate pregnancy plans during postoperative care. However, the small, selected subgroup and post-baseline regimen changes preclude conclusions about comparative fertility benefit. Prospective studies should assess symptom control, time to pregnancy, and live birth following this transition.

Clinical implications

These findings may inform individualized treatment even when short-term pain improvement and ovarian endometrioma recurrence do not clearly distinguish the regimens. Dydrogesterone may be considered when cyclic bleeding is preferred or mood or sleep-related adverse effects are a particular concern. Dienogest may be considered when the absence of bleeding is preferred, with counseling about irregular

bleeding early in treatment. Treatment choice should also be revisited as reproductive goals change. Luteal-phase dydrogesterone may offer a management option for women who wish to attempt conception while continuing treatment for symptoms, although outcomes after this transition require further study.

Strengths and limitations

The prospective multicenter design, high follow-up retention, and standardized outcome assessment strengthened the direct comparison. Prespecified covariate adjustment addressed measured baseline differences, and sensitivity analyses yielded consistent estimates for the primary outcome. However, treatment selection during routine care may have introduced confounding by indication. The unadjusted 24-week VAS difference decreased from 0.50 points to approximately zero after adjustment for baseline pain and other prespecified covariates, although the direction and magnitude of residual confounding remain uncertain. Missing biomarker data remained a limitation despite consistent imputation analyses. The 24-week follow-up limited assessment of long-term recurrence, while the small pregnancy subgroup and subsequent treatment changes restricted interpretation of reproductive outcomes.

Conclusions

In conclusion, adjusted 24-week VAS pain-score changes did not clearly differ between dydrogesterone and dienogest after laparoscopic cystectomy for ovarian endometrioma. Dydrogesterone was associated with greater improvement in mental health-related quality of life and fewer reports of anxiety or depression and insomnia, while bleeding patterns differed between regimens. No clear between-group

differences were observed in CA-125, AMH, or short-term recurrence. These findings may inform individualized postoperative treatment, while comparative studies with longer follow-up are needed to assess sustained symptom control, recurrence, and reproductive outcomes.

List of abbreviations

AMH: anti-Müllerian hormone; BH: Benjamini – Hochberg; BMI: body mass index; CA-125: cancer antigen 125; CI: confidence interval; CMSS: Cox Menstrual Symptom Scale; DIE: deep infiltrating endometriosis; DNG: dienogest; EHP-30: Endometriosis Health Profile-30; GnRH: gonadotropin-releasing hormone; HC3: heteroscedasticity-consistent covariance matrix estimator, type 3; IQR: interquartile range; MCS: Mental Component Summary; PCS: Physical Component Summary; rASRM: revised American Society for Reproductive Medicine; SF-12: 12-Item Short Form Health Survey;SMD: standardized mean difference; VAS: visual analog scale.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Guangdong Women and Children Hospital (approval No. GuangdongWCH[202301128]).

Consent to participate

Written informed consent to participate was obtained from all participants before enrollment.

Clinical trial number

Clinical trial number: not applicable. This was a prospective observational cohort study in which treatment was selected during routine clinical care. The study was registered at ClinicalTrials.gov (NCT05976529; first submitted for registration on 25 April 2023).

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to patient confidentiality and institutional data protection requirements but are available from the corresponding author on reasonable request, subject to institutional approval.

Competing interests

LL reports institutional grant support for the submitted work, paid to Guangdong Women and Children Hospital, from the Department of Science and Technology of Guangdong Province, the Natural Science Foundation of Guangdong Province, and the Beijing Medical and Health Public Welfare Foundation. The other authors declare no competing interests.

Funding

This work was supported by the Department of Science and Technology of Guangdong Province through the Guangdong–Hong Kong–Macao Greater Bay Area International Science and Technology Innovation Center Program (grant No.

2024A0505090001); the Natural Science Foundation of Guangdong Province (grant No. 2024A1515013145); and the Beijing Medical and Health Public Welfare Foundation (grant No. YWJKJJHKYJJ-PNFM2603). The funders had no role in the study design, data collection, data analysis, interpretation of the results, manuscript preparation, or the decision to submit the manuscript for publication.

Authors' contributions

JL: data curation, investigation, writing – original draft; WL: formal analysis, methodology, writing – original draft, writing – review and editing; HM: formal analysis, methodology; XL: data curation, investigation; XZ: data curation, investigation; MZ: data curation, investigation; LL: conceptualization, methodology, resources, supervision, writing – review and editing.

Acknowledgements

The authors thank the clinical and research staff at Guangdong Women and Children Hospital, Zhongshan Bo'ai Hospital, Longgang Central Hospital of Shenzhen, and the First People's Hospital of Foshan for their assistance with participant recruitment, study coordination, data collection, and follow-up management.

References

[1] Nezhat FR, Cathcart AM, Nezhat CH, Nezhat CR. Pathophysiology and Clinical Implications of Ovarian Endometriomas. Obstet Gynecol. 2024;143(6):759-66.

[2] Becker CM, Bokor A, Heikinheimo O, Horne A, Jansen F, Kiesel L, et al. ESHRE guideline: endometriosis. Hum Reprod Open. 2022;2022(2):hoac009.

[3] Younis JS, Shapso N, Ben-Sira Y, Nelson SM, Izhaki I. Endometrioma surgery-a systematic review and meta-analysis of the effect on antral follicle count and anti-Müllerian hormone. Am J Obstet Gynecol. 2022;226(1):33-51.e7.

[4] Tucker DR, Noga HL, Lee C, Chiu DS, Bedaiwy MA, Williams C, et al. Pelvic pain comorbidities associated with quality of life after endometriosis surgery. Am J Obstet Gynecol. 2023;229(2):147.e1-.e20.

[5] Veth VB, Keukens A, Reijs A, Bongers MY, Mijatovic V, Coppus S, et al. Recurrence after surgery for endometrioma: a systematic review and meta-analyses. Fertil Steril. 2024;122(6):1079-93.

[6] Burghaus S, Schäfer SD, Bär KJ, Bartley J, Beckmann MW, Behrens A, et al. Diagnosis and Therapy of Endometriosis. Guideline of the DGGG, OEGGG and SGGG (S2k-Level, AWMF Registry No. 015/045, April 2025). Geburtshilfe Frauenheilkd. 2026;86(2):133-88.

[7] Piacenti I, Tius V, Viscardi MF, Biasioli A, Arcieri M, Restaino S, et al. Dienogest vs. combined oral contraceptive: A systematic review and meta-analysis of efficacy and side effects to inform evidence-based guidelines. Acta Obstet Gynecol Scand. 2025;104(8):1424-32.

[8] Muzii L, Di Tucci C, Galati G, Carbone F, Palaia I, Bogani G, et al. The Efficacy of Dienogest in Reducing Disease and Pain Recurrence After Endometriosis Surgery: a Systematic Review and Meta-Analysis. Reprod Sci. 2023;30(11):3135-43.

[9] Li RR, Xi Q, Tao L, Sheng W, Zhao CC, Wu YJ. A systematic review and Bayesian analysis of the adverse effects of dienogest. BMC Pharmacol Toxicol. 2024;25(1):43.

[10] Klipping C, Duijkers I, Remmers A, Faustmann T, Zurth C, Klein S, et al. Ovulation-inhibiting effects of dienogest in a randomized, dose-controlled pharmacodynamic trial of healthy women. J Clin Pharmacol. 2012;52(11):1704-13.

[11] Sukhikh GT, Adamyan LV, Dubrovina SO, Baranov, II, Bezhenar VF, Kozachenko AV, et al. Prolonged cyclical and continuous regimens of dydrogesterone are effective for reducing chronic pelvic pain in women with endometriosis: results of the ORCHIDEA study. Fertil Steril. 2021;116(6):1568-77.

[12] Kitawaki J, Koga K, Kanzo T, Momoeda M. An assessment of the efficacy and safety of dydrogesterone in women with ovarian endometrioma: An open-label multicenter clinical study. Reprod Med Biol. 2021;20(3):345-51.

[13] Overton CE, Lindsay PC, Johal B, Collins SA, Siddle NC, Shaw RW, et al. A randomized, double-blind, placebo-controlled study of luteal phase dydrogesterone (Duphaston) in women with minimal to mild endometriosis. Fertil Steril. 1994;62(4):701-7.

[14] Li Y, Kang B, Zhao X, Cui X, Chen J, Wang L. Association between depression and dysmenorrhea among adolescent girls: multiple mediating effects of binge eating and sleep quality. BMC Womens Health. 2023;23(1):140.

[15] Ware JE, Jr., Kosinski M, Turner-Bowker DM, Gandek B. How to score version 2 of the SF-12 Health Survey (with a supplement documenting version 1). Lincoln, RI: QualityMetric Incorporated; 2002.

[16] Aslan O, Yildiz S, Kaya C, Altinay S, Aydiner IE, Karabulut E, et al. Progesterone receptor B over progesterone receptor A prevents recurrence in bilateral endometriomas. Rev Assoc Med Bras (1992). 2024;70(9):e20240485.

[17] Revised American Society for Reproductive Medicine classification of endometriosis: 1996. Fertil Steril. 1997;67(5):817-21.

[18] Piacenti I, Viscardi MF, Masciullo L, Sangiuliano C, Scaramuzzino S, Piccioni MG, et al. Dienogest versus continuous oral levonorgestrel/EE in patients with endometriosis: what's the best choice? Gynecol Endocrinol. 2021;37(5):471-5.

[19] Global fertility in 204 countries and territories, 1950-2021, with forecasts to 2100: a comprehensive demographic analysis for the Global Burden of Disease Study 2021. Lancet. 2024;403(10440):2057-99.

[20] When more is not better: 10 'don'ts' in endometriosis management. An ETIC (*) position statement. Hum Reprod Open. 2019;2019(3):hoz009.

[21] Abdul Karim AK, Abd Aziz NH, Md Zin RR, Mohd Mokhtar N, Shafiee MN. The Effect of Surgical Intervention of Endometriosis to CA-125 and Pain. Malays J Med Sci. 2020;27(6):7-14.

[22] Lee JH, Song JY, Yi KW, Lee SR, Lee DY, Shin JH, et al. Effectiveness of Dienogest for Treatment of Recurrent Endometriosis: Multicenter Data. Reprod Sci. 2018;25(10):1515-22.

[23] Techatraisak K, Hestiantoro A, Soon R, Banal-Silao MJ, Kim MR, Seong SJ, et al. Impact of Long-Term Dienogest Therapy on Quality of Life in Asian Women with Endometriosis: the Prospective Non-Interventional Study ENVISIOeN. Reprod Sci. 2022;29(4):1157-69.

[24] Polis CB, Hussain R, Berry A. There might be blood: a scoping review on women's responses to contraceptive-induced menstrual bleeding changes. Reprod Health. 2018;15(1):114.

[25] Nirgianakis K, Vaineau C, Agliati L, McKinnon B, Gasparri ML, Mueller MD. Risk factors for non-response and discontinuation of Dienogest in endometriosis patients: A cohort study. Acta Obstet Gynecol Scand. 2021;100(1):30-40.

[26] Murdock C, Murdock C, Sanchez-Ramos L, McKinney JA, Carrubba AR, Lewis G. The Impact of Laparoscopic Cystectomy for Ovarian Endometrioma on Anti-Müllerian Hormone Levels: A Systematic Review and Meta-Analysis. Gynecol Obstet Invest. 2025;90(6):657-71.

[27] Weng SS, Wang YL, Chuang FC, Sun FJ. Effect of dienogest on serum anti-Mullerian hormone level after laparoscopic cystectomy of ovarian endometrioma. Taiwan J Obstet Gynecol. 2023;62(4):521-4.

[28] Muraoka A, Osuka S, Yabuki A, Bayasula, Yoshihara M, Tanaka H, et al. Impact of perioperative use of GnRH agonist or dienogest on ovarian reserve after cystectomy for endometriomas: a randomized controlled trial. Reprod Biol Endocrinol. 2021;19(1):179.

[29] Testing and interpreting measures of ovarian reserve: a committee opinion. Fertil Steril. 2020;114(6):1151-7.

Table 1. Baseline characteristics by initial treatment group

Characteristic	Overall (N=242)	Dydrogesterone (n=109)	Dienogest (n=133)	SMD
Demographic characteristics				
Age, years	33.00 (29.00, 39.00)	32.00 (28.00, 36.00)	35.00 (29.00, 41.00)	0.266
BMI, kg/m²	21.44 (19.52, 23.59)	21.93 (19.40, 24.70)	21.10 (19.72, 23.23)	0.228
Study center				1.115
Guangdong Women and Children Hospital	89 (36.8)	16 (14.7)	73 (54.9)	
Zhongshan Bo'ai Hospital	67 (27.7)	51 (46.8)	16 (12.0)	
Shenzhen Longgang Central Hospital	69 (28.5)	30 (27.5)	39 (29.3)	
The First People's Hospital of Foshan	17 (7.0)	12 (11.0)	5 (3.8)	
Reproductive and menstrual characteristics				
Parity ≥1	136（56.2）	47（43.1）	89（66.9）	0.493
Infertility, yes	27 (11.2)	23 (21.1)	4 (3.0)	0.578
Fertility intention, yes	68 (28.1)	43 (39.4)	25 (18.8)	0.467
Menstrual cycle length, days	30.00 (28.00, 30.00)	28.00 (28.00, 30.00)	30.00 (28.00, 30.00)	0.074
Menstrual bleeding duration, days	7.00 (5.00, 7.00)	7.00 (5.00, 7.00)	7.00 (5.00, 7.00)	0.076
Pain symptoms and patient-reported outcomes				
VAS pain score	5.00 (3.00, 6.75)	5.00 (3.00, 6.00)	5.00 (3.00, 7.00)	0.113
CMSS score	18.00 (10.00, 30.00)	16.00 (8.00, 26.00)	20.00 (11.00, 31.00)	0.150
SF-12 PCS score	45.00 (36.34, 52.94)	45.68 (39.46, 52.00)	44.81 (31.41, 55.00)	0.147
SF-12 MCS score	55.91 (45.51, 64.00)	56.39 (47.61, 64.00)	55.08 (45.02, 64.00)	0.121
Disease and laboratory characteristics				
rASRM score	36.00 (24.00, 62.00)	37.00 (25.00, 65.00)	35.00 (24.00, 60.00)	0.115

Ovarian cyst diameter, cm	6.50 (4.93, 8.20)	6.00 (4.90, 7.90)	6.70 (5.00, 8.60)	0.250
Deep infiltrating endometriosis, yes	58 (24.0)	21 (19.3)	37 (27.8)	0.203
CA-125, U/mL	52.50 (35.89, 88.29)	49.60 (34.30, 78.10)	55.60 (36.40, 94.80)	0.162
AMH, ng/mL	2.33 (1.14, 3.58)	2.33 (1.31, 3.58)	2.24 (1.08, 3.58)	0.082

530 Data are presented as median (IQR) or n (%). SMDs are reported as absolute values; values ⩾0.10

531 indicate potential imbalance. No baseline data were missing.

532 Abbreviations: AMH, anti-Müllerian hormone; BMI, body mass index; CA-125, cancer antigen 125;

533 CMSS, Cox Menstrual Symptom Scale; MCS, Mental Component Summary; PCS, Physical

534 Component Summary; rASRM, revised American Society for Reproductive Medicine; SF-12, 12-Item

535 Short Form Health Survey; SMD, standardized mean difference; VAS, visual analog scale.

536

537 **Table 2.** Between-group differences in change from baseline in VAS pain score

Time point	N, total (dydrogesterone/DNG)	Unadjusted mean difference (95% CI)	Adjusted mean difference (95% CI)	Adjusted *P* value
12 weeks	238 (106/132)	0.42 (−0.10, 0.94)	0.11 (−0.35, 0.56)	0.647
24 weeks	234 (105/129)	0.50 (−0.08, 1.08)	0.00 (−0.44, 0.43)	0.983

538 The 24-week analysis was primary; the 12-week analysis was supportive. Estimates represent

539 between-group differences (dydrogesterone minus dienogest) in change from preoperative baseline;

540 negative values indicate greater pain reduction with dydrogesterone. Unadjusted estimates were

541 obtained from linear models of VAS change with treatment group as the sole predictor. Adjusted

542 estimates were obtained from analysis-of-covariance models controlling for baseline VAS score and

543 prespecified covariates. HC3 heteroscedasticity-consistent standard errors were used. P values

544 correspond to adjusted analyses and are two-sided.

545 Abbreviations: CI, confidence interval; DNG, dienogest; VAS, visual analogue scale.

546

547

548

549

550

551

552

553

554

555 **Table 3.** Patient-reported and biomarker outcomes at 12 and 24 weeks

Outcome	Time point	Participants, n (dydrogesterone/DNG)	Adjusted estimate (95% CI)[a]	Nominal *P* value	BH-adjusted *P* value
CMSS score	12 weeks	238 (106/132)	−4.95 (−10.12, 0.23)	0.061	0.183
	24 weeks	234 (105/129)	−0.13 (−2.05, 1.79)	0.894	0.930
SF-12 PCS score	12 weeks	238 (106/132)	−0.10 (−2.25, 2.06)	0.930	0.930
	24 weeks	234 (105/129)	−0.15 (−2.22, 1.92)	0.884	0.930
SF-12 MCS score	12 weeks	238 (106/132)	1.94 (−1.36, 5.25)	0.248	0.497
	24 weeks	234 (105/129)	5.32 (2.28, 8.35)	<0.001	0.004
CA-125, U/mL	24 weeks	176 (83/93)	1.07 (0.90, 1.27)	0.472	0.880
AMH, ng/mL	24 weeks	187 (85/102)	1.02 (0.79, 1.33)	0.880	0.880

556 [a] For CMSS, PCS, and MCS, estimates are adjusted mean differences in change from baseline
557 (dydrogesterone minus DNG); lower CMSS and higher PCS and MCS scores indicate improvement.
558 CA-125 and AMH were analysed on the natural-log scale; estimates are geometric mean ratios
559 (dydrogesterone/DNG) from complete-case analyses. Models were adjusted for the corresponding
560 baseline value and prespecified covariates, with HC3 heteroscedasticity-consistent standard errors.
561 Benjamini – Hochberg adjustment was applied separately to the six patient-reported outcome
562 comparisons and the two biomarker comparisons; 95% CIs were not adjusted for multiplicity. All P
563 values are two-sided.

564 Abbreviations: AMH, anti-Müllerian hormone; BH, Benjamini – Hochberg; CA-125, cancer antigen

125; CI, confidence interval; CMSS, Cox Menstrual Symptom Scale; DNG, dienogest; MCS, Mental Component Summary; PCS, Physical Component Summary; SF-12, 12-Item Short Form Health Survey.

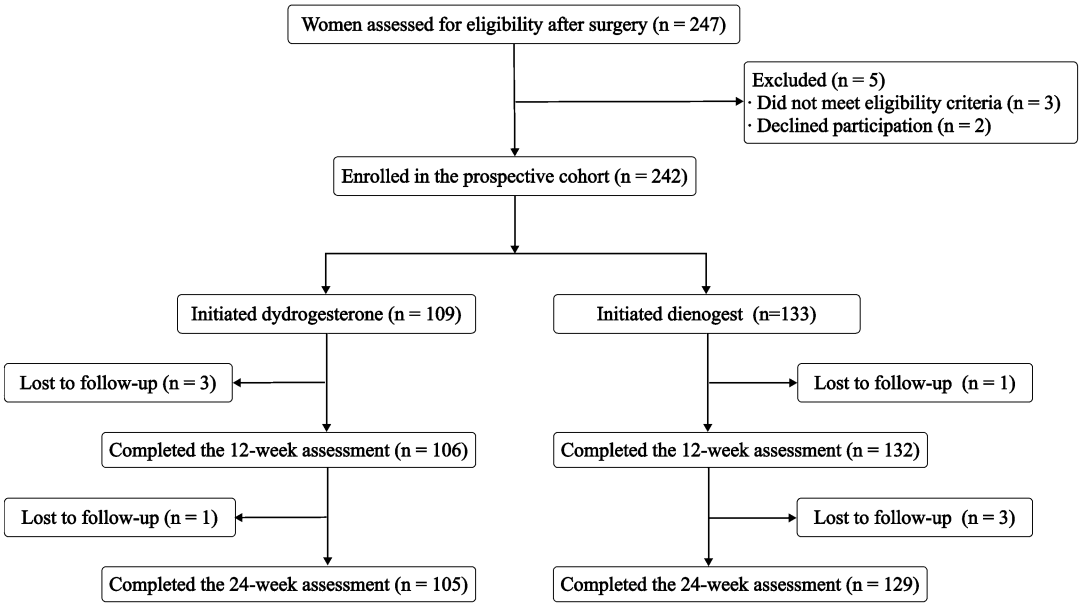


Figure 1. Study flow diagram.

Participant screening, enrollment, treatment initiation, and follow-up through 24 weeks are shown.

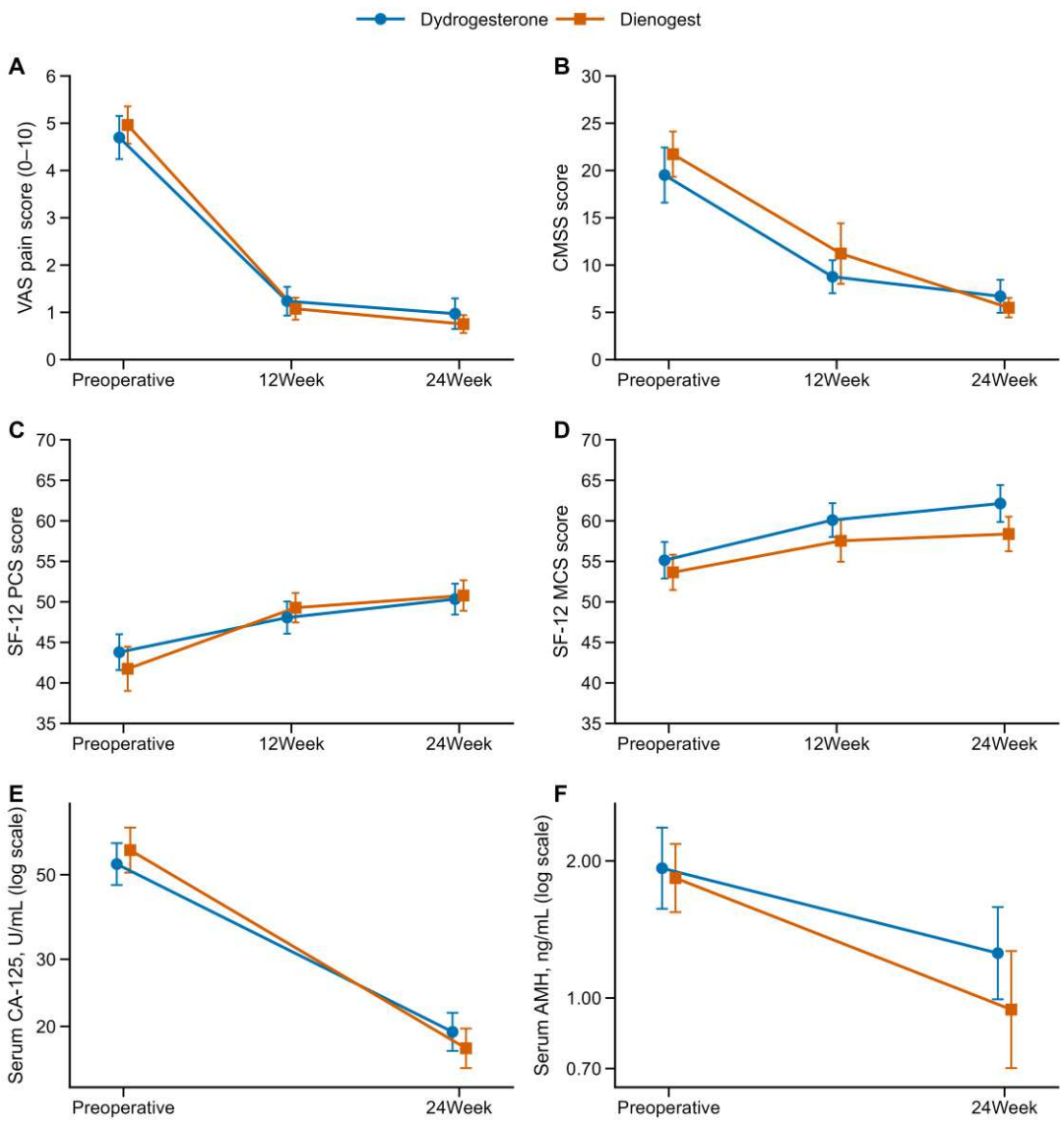
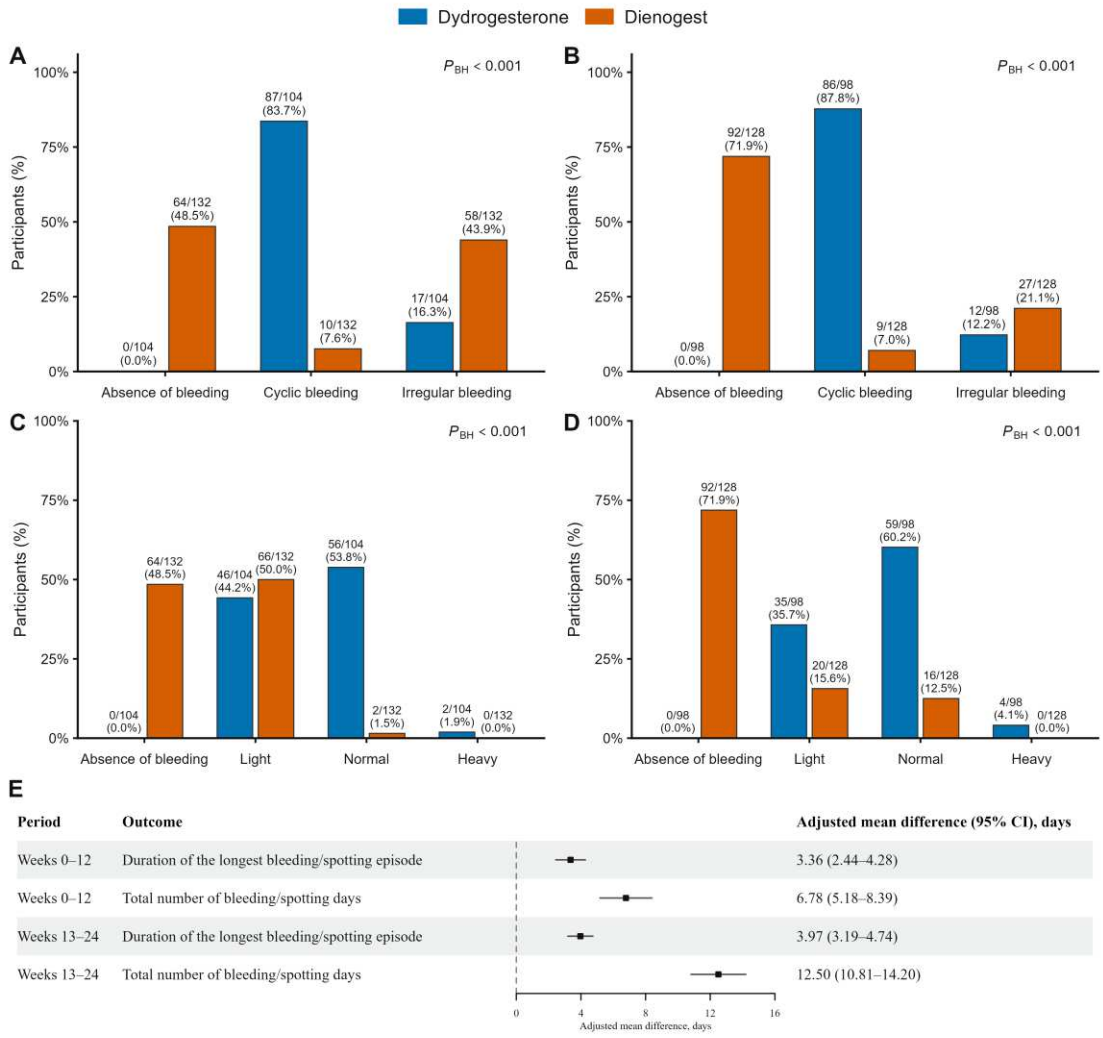


Figure 2. Clinical outcomes by treatment group through week 24.

(A) Visual analog scale (VAS) pain score. (B) Cox Menstrual Symptom Scale (CMSS) score. (C) Physical Component Summary (PCS) and (D) Mental Component Summary (MCS) scores of the 12-Item Short Form Health Survey (SF-12). (E) Serum cancer antigen 125 (CA-125) level. (F) Serum anti-Müllerian hormone (AMH) level.

589 Points represent unadjusted means in panels A-D and unadjusted geometric means in
590 panels E and F; error bars indicate 95% confidence intervals. CA-125 and AMH
591 values are plotted on logarithmic y-axes. Estimates were based on available
592 observations at each time point.

593



594

595 **Figure 3.** Bleeding patterns, volume, and duration during postoperative treatment
596 Panels A and B show bleeding patterns, and panels C and D show bleeding volume,
597 during weeks 0 – 12 (A, C) and 13 – 24 (B, D). Cyclic bleeding was confined to
598 expected bleeding periods: following drug withdrawal in each dydrogesterone cycle

or estimated from the pretreatment menstrual cycle for dienogest. Irregular bleeding included any bleeding or spotting outside these periods, even when cyclic bleeding also occurred. Absence of bleeding indicated no bleeding or spotting throughout the entire 12-week interval.Participants rated bleeding volume as light, normal, or heavy relative to their usual pretreatment menstrual flow.Global P values for panels A – D were calculated using Fisher – Freeman – Halton tests with 100,000 Monte Carlo replicates and adjusted across the four comparisons using the Benjamini – Hochberg procedure. Panel E shows adjusted mean differences in the longest bleeding/spotting episode and total bleeding/spotting days, expressed as dydrogesterone minus dienogest; positive values indicate longer durations with dydrogesterone. Estimates were derived from separate linear models adjusted for prespecified covariates, with HC3 robust standard errors. Confidence intervals were not adjusted for multiplicity.Analyses included participants with evaluable data for each interval; bleeding outcomes during pregnancy were considered not applicable. All P values are two-sided.

Abbreviation: CI, confidence interval.

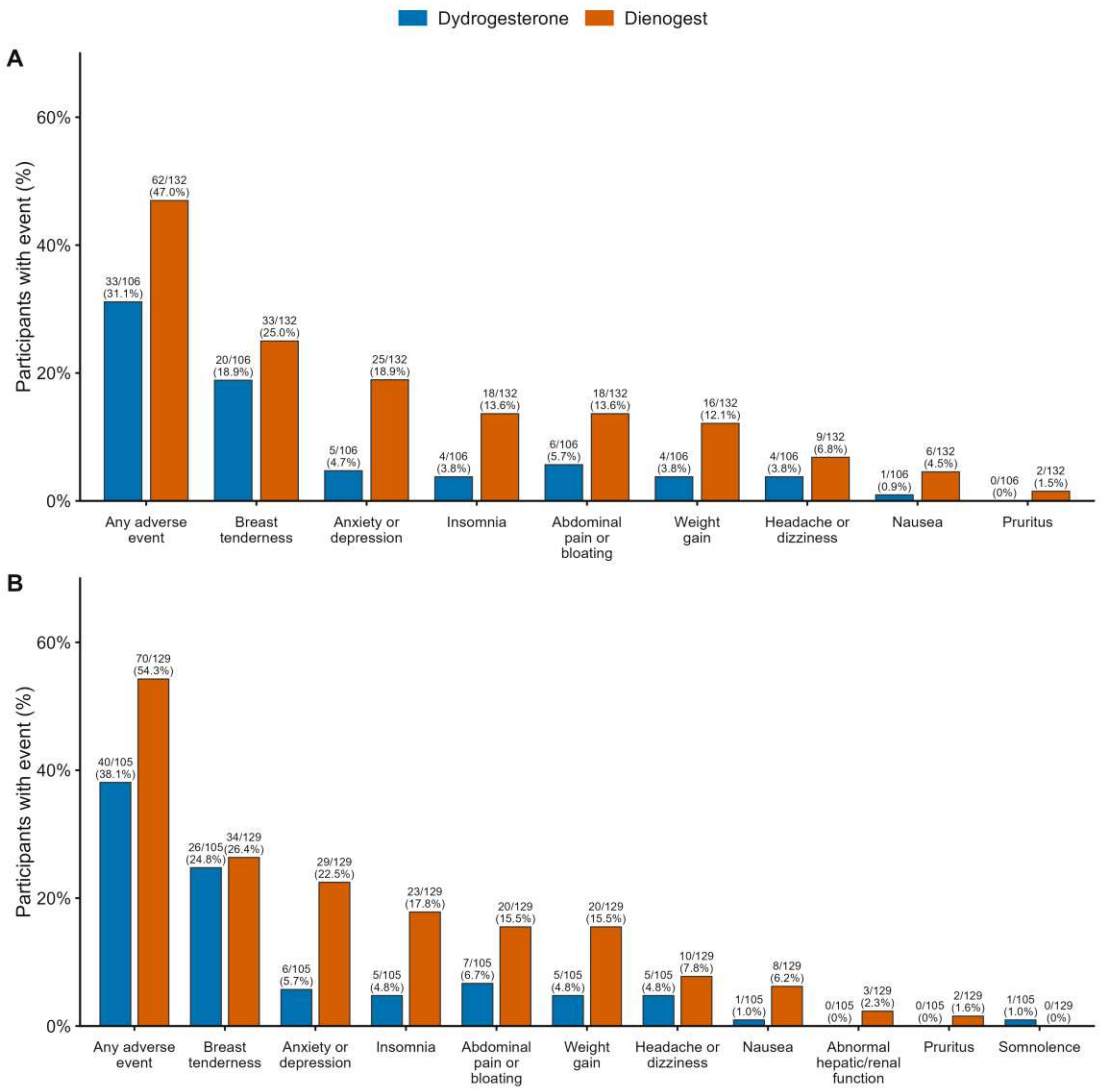


Figure 4. Adverse events through weeks 12 and 24

Panel A shows cumulative adverse events through week 12 and panel B through week 24. Any adverse event denotes at least one assessed event by the corresponding time point. For the week-24 analysis, each participant was counted once per event category if the event occurred during either weeks 0 – 12 or 13 – 24. Denominators include participants with ascertainable status for the relevant event. Abnormal hepatic or renal function was assessed only at week 24.

Supplementary material(.docx).

Supplementary Tables S1 – S4, Supplementary Figures S1 – S3, and Appendix A: SF-12v2 scoring method.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.docx