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Clinical efficacy and safety of indomethacin-gyneFix IUD combined with a levonorgestrel-releasing intrauterine system in patients with adenomyosis and different uterine cavity depths

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Abstract: **Background**: Adenomyosis is commonly associated with dysmenorrhea and heavy menstrual bleeding. Although the levonorgestrel-releasing intrauterine system (Mirena, LNG-IUS) is recommended as a first-line conservative treatment, device displacement or expulsion remains a major limitation, especially in patients with enlarged uteri or deep uterine cavities. **Objectives**: To evaluate the clinical efficacy and safety of the Indomethacin-GyneFix IUD (GyneFix IUD) combined with LNG-IUS in patients with adenomyosis and to assess whether uterine cavity depth influences device stability. **Methods**: In this single-center prospective randomized controlled trial, 270 patients with adenomyosis were randomly assigned in a 1:1:1 ratio to the GyneFix IUD + LNG-IUS group, the ring IUD + LNG-IUS group, or the LNG-IUS-alone group (90 patients each). The primary endpoint was the rate of device displacement/expulsion at 6 months. Secondary endpoints included changes in visual analogue scale (VAS) scores, pictorial blood loss assessment chart (PBAC) scores, uterine volume, hemoglobin (Hb), serum CA125, adverse events and patient acceptance. Subgroup analysis was performed according to uterine cavity depth (≤9cm vs. >9 cm). **Results**: At 6 months, the displacement/expulsion rate was significantly lower in the GyneFix IUD + LNG-IUS group (2.22%) than in the ring IUD + LNG-IUS group (10.00%) and the LNG-IUS-alone group (18.89%) (χ^2=13.468, P<0.001). All three groups showed significant improvement in dysmenorrhea, menstrual blood loss, Hb and CA125 compared with baseline, without significant between-group differences (all P>0.05). Adverse event rates were comparable among groups (all P>0.05). Patient willingness to choose the same treatment again (95.12%) and willingness to recommend it (90.24%) were significantly higher in the GyneFix IUD + LNG-IUS group. In patients with uterine cavity depth >9 cm, the stability advantage of this strategy was more pronounced. **Conclusion**: GyneFix IUD combined with LNG-IUS significantly reduces device displacement/expulsion in adenomyosis, particularly in patients with deeper uterine cavities, while maintaining comparable symptom relief and safety. It may represent a more stable and acceptable long-term conservative treatment option.

Keywords: Adenomyosis; Genetec; Intrauterine device displacement; Levonorgestrel intrauterine system; Randomized controlled trial; Uterine depth

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INTRODUCTION

Adenomyosis (AM) is an estrogen-dependent benign condition caused by the ectopic growth of endometrial tissue into the myometrium, predominantly affecting women of reproductive age. In China, its incidence has shown a gradual upward trend with a tendency toward younger onset (Alson S *et al*., 2024). The primary clinical manifestations include progressively worsening dysmenorrhea, menorrhagia, prolonged menstrual periods and secondary infertility, which significantly impair patients' quality of life and overall health (Wang Q *et al*., 2022). Current treatment approaches for AM have shifted from traditional radical surgical interventions to non-surgical, individualized and diversified methods, particularly for patients who prefer to avoid major surgeries (Zhang B *et al*., 2025). Among various conservative therapies, pharmacotherapy has emerged as a primary treatment option due to its reversibility and minimally invasive nature (Zhang *et al*., 2025; Shen *et al*., 2024).

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The levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena) is a device that slowly and continuously releases levonorgestrel into the body to inhibit endometrial growth, thereby controlling menorrhagia and alleviating pain. It can also serve as an auxiliary diagnostic tool (Chen *et al*., 2025). Multiple authoritative guidelines from domestic and international institutions have recommended the use of LNG-IUS as a first-line treatment for AM (Etrusco A *et al*., 2023). However, clinical observations have shown that LNG-IUS is associated with a relatively high risk of displacement or expulsion in patients with adenomyosis, especially in those with enlarged uteri or deep uterine cavities, which may compromise treatment effectiveness (Yuk JS *et al.*, 2025). Therefore, improving intrauterine device stability has become a key issue in conservative management. Several strategies have been proposed to reduce expulsion risk. For example, gonadotropin-releasing hormone agonists may temporarily reduce uterine volume before device placement (Etrusco A *et al*, 2023). However, this effect is often transient and does not directly solve the mechanical problem of intrauterine device fixation.

In the present study, we evaluated two different mechanical stabilization strategies used in combination with LNG-IUS. The first was the Indomethacin-GyneFix IUD (GyneFix IUD), which served as an anchoring device rather than as a modified LNG-IUS (Che Y *et al*, 2023). The GyneFix IUD is characterized by a flexible frameless structure and a fundal anchoring knot. During placement, the anchoring knot is inserted into the uterine fundal myometrium under ultrasound guidance, allowing the attached LNG-IUS to remain suspended and stabilized within the uterine cavity. This represents an active anchoring strategy.

The second strategy used a ring IUD placed together with LNG-IUS. In contrast to GyneFix IUD, the ring IUD provides passive mechanical support within the uterine cavity but does not anchor into the fundal myometrium. Therefore, its stabilizing mechanism differs fundamentally from that of the GyneFix IUD (Lyman CC *et al*, 2023).

Although preliminary studies have suggested that anchoring-based fixation may improve device stability while maintaining therapeutic efficacy, high-quality prospective randomized evidence remains limited. In addition, the influence of uterine cavity depth, an important anatomical parameter, on device stability under different fixation strategies has not been sufficiently clarified. Therefore, this prospective randomized controlled trial was conducted to compare the GyneFix IUD + LNG-IUS, ring IUD + LNG-IUS and LNG-IUS-alone strategies in patients with adenomyosis and to evaluate whether uterine cavity depth affects device stability.

MATERIALS AND METHODS

Study subjects

This study was designed as a single-center, prospective, parallel-group, randomized controlled clinical trial conducted at Wenzhou People's Hospital, Wenzhou, Zhejiang Province, China, in patients with adenomyosis. The study involved an independent researcher, a study nurse, two senior gynecologists, designated research assistants, ultrasound physicians/sonographers and blinded statisticians. The sample size was calculated based on previously reported 6-month device expulsion rates in patients with adenomyosis (Wang *et al,* 2025), the rate of Menorrhagia (Mirena) device expulsion in patients with adenomyosis is approximately 15%–20% within 6 months and it is estimated that the Jymen double ring can reduce this rate to below 5%. The sample size was calculated using a chi-square test for three-group rate comparison, with a significance level of $\alpha=0.05$ (two-tailed) and a power of $1-\beta=0.80$. Calculations indicated that at least 75 cases per group were required. Considering an attrition rate of 15%–20%, a total of 90 cases per group were planned, resulting in 270 patients across three groups. The study flow chart is shown in Fig.1.

Inclusion criteria: Age 20–55 years, no desire for pregnancy but strong preference for hysterectomy; diagnosed with adenomyosis by transvaginal ultrasound (Harmsen MJ *et al*, 2022), with endometrial glandular or stromal infiltration ≥2 mm; no contraindications to IUD placement; voluntary participation and ability to comply with follow-up. *Exclusion criteria*: Pregnancy or suspected pregnancy; concurrent malignant tumors of the reproductive system, severe cervical lesions or uterine malformations; severe coagulation disorders, hepatic or renal insufficiency; history of hypersensitivity to levonorgestrel, copper or indomethacin; uncontrolled pelvic inflammatory disease or vaginal infection; uterine prolapse ≥grade II; inability to complete follow-up or incomplete data. This study was reviewed and approved by the institutional ethics committee (KY-2023-200). All participants signed informed consent forms.

Randomization and allocation concealment

Using a computer-generated random number sequence, eligible patients were divided into three groups in a 1:1:1 ratio. The random sequence was generated and sealed by an independent researcher who was not involved in patient recruitment, treatment, follow-up, or assessment. After written informed consent was obtained, the study nurse sequentially opened the numbered opaque envelopes according to the order of enrollment to determine the patient's group assignment.

Because the three interventions involved different device configurations and implantation procedures, complete blinding of patients and operating gynecologists was not fully feasible in practice. However, patients were not routinely informed of the specific device type assigned and all groups underwent intrauterine treatment under similar perioperative conditions, which helped reduce expectation-related performance bias.

Postoperative outcome assessors were blinded to treatment allocation. Follow-up data collection, including symptom assessment, satisfaction questionnaires and medical record extraction, was performed by designated research assistants who were not involved in treatment assignment and were unaware of group allocation. In addition, the statisticians were blinded to treatment identity during the primary analysis by using coded group labels.

Ultrasound physicians could not be blinded because the type of intrauterine device was identifiable on ultrasound imaging. To minimize potential detection bias, all ultrasound examinations were performed using a prespecified standardized protocol, the same ultrasound equipment and unified objective diagnostic criteria for device position and uterine measurements. In addition, the sonographers were not involved in randomization, treatment allocation, postoperative symptom assessment, questionnaire administration, or statistical analysis.

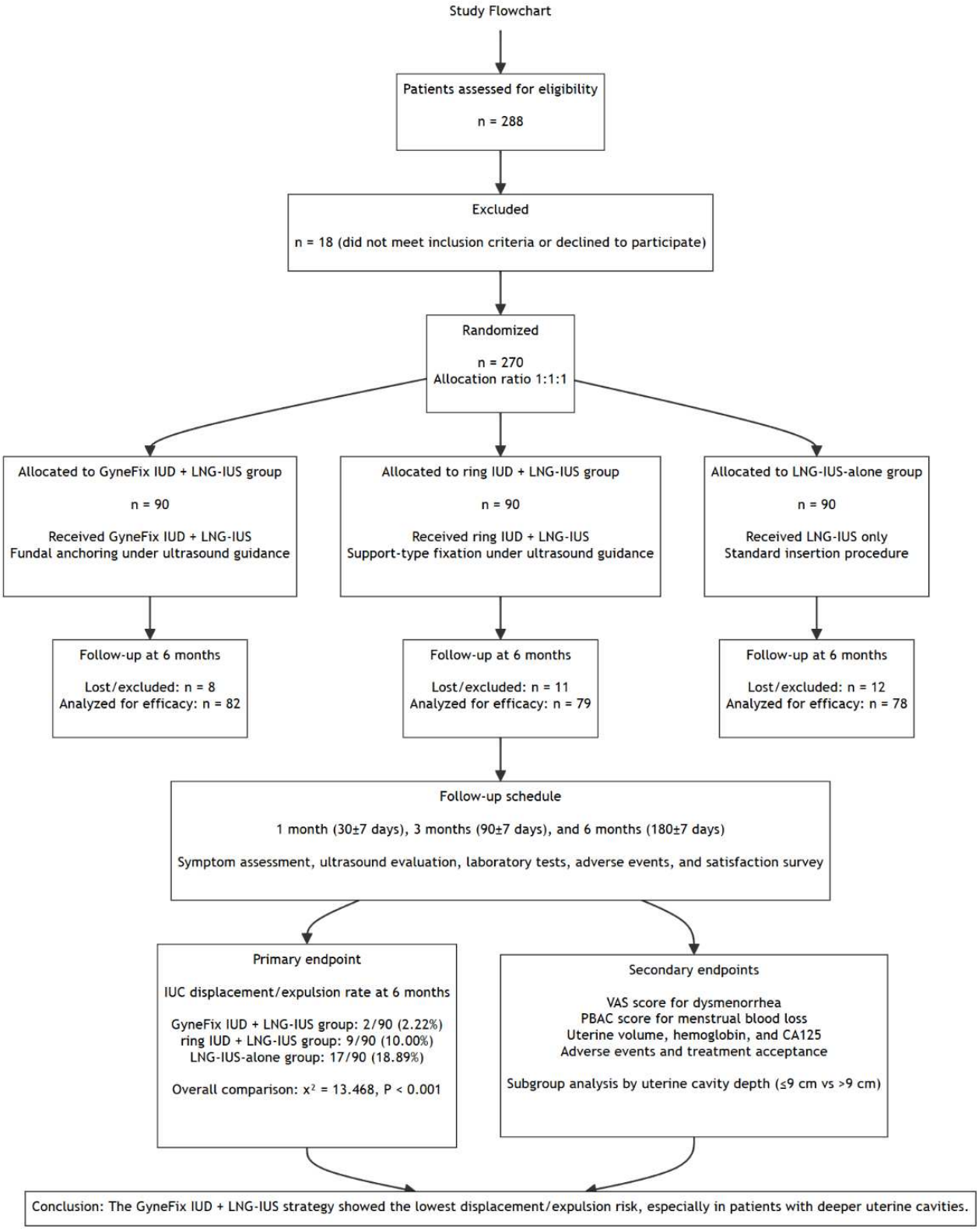

Fig. 1: Study flow chart

Surgical procedure standards

Preoperative preparation

All patients underwent preoperative examinations including complete blood count (CBC), coagulation function, liver and kidney function tests, vaginal discharge routine examination, electrocardiogram (ECG) and

gynecological ultrasound to exclude surgical contraindications. The procedures were performed by two senior gynecologists with advanced professional titles who were proficient in various IUD insertion techniques.

Timing of surgery and anesthesia

The procedure should be performed within 7 days of the onset of menstruation, avoiding periods of heavy menstrual flow to facilitate cervical dilation and ensure the patient is not pregnant. Based on the patient's preference and cervical conditions, two methods may be employed: (1) Local anesthesia: injection of 2mL of 1% lidocaine at the 3 o'clock and 9 o'clock positions of the cervix; (2) Intravenous anesthesia: intravenous administration of propofol under the supervision of an anesthesiologist.

Placement method

All procedures were performed under real-time ultrasound guidance using the BELSON760E fully digital color ultrasound monitoring system. The procedures were conducted by two senior gynecologists experienced in intrauterine device insertion. Patients underwent routine preoperative assessment to exclude contraindications to intrauterine manipulation. Postoperative adverse events, including pain, bleeding, pelvic infection, uterine perforation, device displacement/expulsion and symptom-driven removal, were prospectively monitored throughout follow-up.

1) *GyneFix IUD + LNG-IUS group*

In this group, the Indomethacin-GyneFix IUD (GyneFix IUD) was used as an anchoring device to stabilize the LNG-IUS (Mirena). A 3-0 non-absorbable surgical suture was used to connect the transverse and vertical arms of the LNG-IUS to the upper portion of the GyneFix IUD. The LNG-IUS was thus suspended from the GyneFix IUD rather than structurally modified. After uterine cavity sounding, the insertion device was advanced to the fundus under ultrasound guidance. The anchoring knot at the apex of the GyneFix IUD was then implanted into the uterine fundal myometrium using the dedicated inserter. Successful anchoring was judged by the operator's tactile feedback and ultrasound confirmation of correct fundal fixation. The tail thread was then released and the inserter was withdrawn. The string was trimmed to 1.5–2.0 cm beyond the external cervical os.

This intervention represented an anchoring-based fixation strategy, in which the GyneFix IUD provided active fundal fixation for the LNG-IUS.

2) *Ring IUD + LNG-IUS group*

In this group, the ring IUD and the LNG-IUS were sequentially inserted into the uterine cavity under ultrasound guidance. The ring IUD was positioned near the upper uterine cavity/fundal region to provide mechanical support for the LNG-IUS. The LNG-IUS was then released in the conventional manner with its transverse arms extended. This intervention represented a support-based fixation strategy, in which the ring IUD provided passive intrauterine support without myometrial anchoring.

3) *LNG-IUS-alone group*

In this group, the LNG-IUS (Mirena) was inserted according to the manufacturer's standard instructions. Correct placement required full extension of the transverse arms and positioning of the device at the uterine fundus under ultrasound guidance.

Postoperative management and follow-up plan

All patients received routine postoperative symptomatic treatment as clinically indicated. They were informed that mild lower abdominal discomfort and spotting might occur after the procedure. Sexual intercourse and tub bathing were avoided for 2 weeks. Patients were instructed to return to the hospital immediately if severe abdominal pain, fever, or heavy vaginal bleeding occurred. Scheduled follow-up visits were conducted at 1 month, 3 months and 6 months after the procedure and included symptom assessment, gynecological examination, ultrasound evaluation and laboratory testing.

Follow-up and evaluation indicators

Follow-up time points

At 30±7 days (1 month), 90±7 days (3 months) and 180±7 days (6 months) post-implantation regular outpatient follow-ups were conducted monthly. All follow-ups were performed by designated research assistants who were not involved in the grouping.The information was collected and followed up with the help of structured interview form and medical record system.

Follow-up content and assessment tools

(1) Baseline and general data collection: Record and verify the patient's age, height, weight at enrollment, body mass index (BMI), menstrual history (cycle length, duration), pregnancy and childbirth history (number of pregnancies, number of deliveries, number of miscarriages), preoperative pretreatment with gonadotropin-releasing hormone agonists (GnRH-a) and presence of IUD history of IUC descent or detachment and comorbid conditions such as uterine fibroids. (2) Symptomatology assessment: (1) Severity of dysmenorrhea:Scoring was performed using the Visual Analogue Scale (VAS) (He S *et al*, 2022). A 10 cm-long strip was used.The scale, with "0 points" (no pain) and "10 points" (intolerable severe pain) marked at both ends, is used by the affected. The severity of pain was rated based on the most severe pain level during the previous menstrual cycle. A score decrease of ≥3 points was defined as "Significant relief". (2) Menstrual blood loss was assessed using the pictorial blood loss assessment chart (PBAC). A reduction of at least 50% from baseline was considered clinically significant (Ko JKY *et al*, 2021). (3) Bleeding pattern recording: Accurately record the number

of days of vaginal bleeding and spotting during the period from postoperative to each follow-up visit. Amenorrhea is defined as no bleeding or spotting for 90 consecutive days (Gynecologic Endocrinology Subgroup *et al*, 2024). (3) Gynecological ultrasound examination: performed by the same senior specialist. The sonographer performed transvaginal examinations and recordings using the same ultrasound equipment (Voluson E10, GE Healthcare): (1) Uterine morphological indicators: Measure the three-dimensional diameters of the uterus (length, width, anteroposterior diameter) and calculate the volume according to the formula (volume =0.523×length×width×anterior-posterior diameter) to calculate uterine volume. (2) Endometrial thickness: measured in the sagittal plane of the uterus maximum thickness of the endometrium. (3) Evaluation of IUD position: The diagnostic criterion for downward displacement is that the upper edge of the IUC does not adhere to the uterine wall. The distance from the base of the IUC or the top of the IUC to the serosal layer of the uterine fundus is>2.0 cm, or the lower edge of the IUC reaches the level of the internal os of the cervix or the positioning of the Gine line knot requires precise measurement of the vertical distance between the Gine line knot at the apex of the uterus and the serosal layer of the uterus(K-S distance), used to evaluate its fixation stability. The detachment was not detected by intrauterine ultrasound imaging. Ovarian monitoring record whether new ovarian cysts are detected, defined as cystic structures with a diameter ≥2.5 cm. (4) Experimental Laboratory tests: (1) Hemoglobin (Hb): Venous blood is collected and analyzed using a fully automated hematology analyzer. Assess the improvement of anemia. (2) Serum Cancer Antigen 125(CA125) level: Collect venous blood and use electrochemiluminescence immunoassay epidemiological analysis for detection. Changes in CA125 levels are used to indirectly reflect the activity of adenomyosis lesions. (5)Adverse Event Monitoring and Documentation: Utilize predefined adverse event record forms to proactively inquire about and document IUC-related incidents. Events included descent, detachment and removal for indication. Bleeding-related events included irregular vaginal bleeding/drip bleeding.The duration and impact on daily life. Local and systemic symptoms include low back pain, lower abdominal distension, increased vaginal discharge, pelvic inflammation (based on CDC diagnostic criteria (Hazra A *et al.*, 2022), cervical motion tenderness/adnexal tenderness + at least one of the following: body temperature>38.3°C, WBC>10×10^9/L, imaging findings suggestive of inflammatory mass), breast tenderness, acne. Metabolic and body shape changes were body weight increase>2.5kg compared to preoperative levels. (6) Treatment acceptance and satisfaction survey: At 6-month postoperative follow-up, the questionnaire was administered using a 5-point Likert scale by self-developed questionnaire (very unwilling, unwilling, neutral, willing, very willing).Survey: "If you had to choose again, would you be willing to undergo this treatment once more?" "Would you be willing to undergo this recommendations for treatment to friends or family members with similar conditions?

Data management and quality control

All follow-up data were entered independently by two people using electronic case report forms (eCRF) and underwent logical validation.Conformity checks were conducted. The principal investigator performed regular data audits. The dropout criteria were defined as loss to follow-up or voluntary withdrawal. The patient was required to withdraw from the study and the IUD was forcibly removed or the patient was referred for surgical treatment due to serious adverse events.

Handling of missing data: Missing data were primarily due to loss to follow-up or withdrawal during the 6-month observation period. For the primary endpoint (IUC displacement/expulsion at 6 months), all randomized patients were retained in the denominator according to their originally assigned groups and patients without complete 6-month outcome confirmation were treated as missing for outcome ascertainment in the main descriptive follow-up dataset. For repeated secondary endpoints, including VAS, PBAC, uterine volume, Hb and CA125, analyses were based on available cases among patients who completed the corresponding follow-up assessments and no imputation of missing values was performed. The number of patients included in each analysis set was reported in the Results and table notes where applicable.

Primary and secondary end points

Primary endpoint: Comparison of IUC displacement/implantation failure rates among the three groups at 6 months postoperatively. Secondary endpoints: Changes and intergroup comparisons of VAS scores for dysmenorrhea, PBAC scores, uterine volume, hemoglobin levels and CA125 levels at 1, 3 and 6 months postoperatively versus baseline. Incidence of adverse reactions within 6 months postoperatively. Patient treatment acceptance at 6 months postoperatively. Subgroup analysis based on uterine depth (defined as ≤9 cm) to investigate the relationship between uterine depth and different IUC displacement risks.

Statistical analysis

Data analysis was performed using SPSS 23.0 software. Measurement data were expressed as mean ± standard deviation, with intergroup comparisons conducted using t-test or one-way analysis of variance (ANOVA); count data were expressed as rates and analyzed using the χ^2 test or Fisher's exact test; ordinal data were analyzed using the rank-sum test. The primary analysis was performed on a per-protocol basis, including patients who completed the assigned intervention and follow-up assessments. Subgroup analysis according to uterine cavity depth (≤9 cm

vs >9 cm) was pre-specified based on its potential clinical relevance to device stability. When the overall intergroup comparison was statistically significant, post-hoc pairwise comparisons were performed using Bonferroni-adjusted tests to control the family-wise type-I error rate. For three-group categorical outcomes, pairwise χ^2 comparisons were interpreted with Bonferroni correction as appropriate. The Kaplan–Meier method was employed to calculate the contraceptive device retention rate and group differences were assessed using the log-rank test. A two-sided *P-value* <0.05 was considered statistically significant.

RESULTS

Patient baseline data

A total of 288 patients were enrolled in this study, with 18 excluded due to non-compliance with inclusion criteria or refusal to participate. Ultimately, 270 patients completed randomization and were included in the analysis, with 90 cases each in the GyneFix IUD + LNG-IUS group, ring IUD + LNG-IUS group and LNG-IUS-alone group. By the 6-month postoperative follow-up, 31 patients were lost to follow-up (8 cases in the GyneFix IUD + LNG-IUS group, including 6 lost to follow-up; 11 cases in the Yuanman double-loop group, including 1 lost to follow-up and 1 case of uterine perforation; 12 cases in the LNG-IUS-alone group). During follow-up, some patients underwent IUC repositioning (lowered to the upper end or not intervened) or were observed without intervention and these were not included in the analysis. The total dropout rate was 11.48%. No statistically significant differences were observed among the three groups in baseline characteristics such as age, BMI, pregnancy and childbirth history and uterine cavity depth (P>0.05), indicating comparability (see Table 1).

For outcome analyses, the primary endpoint was assessed in the randomized cohort according to group allocation, whereas secondary efficacy and laboratory outcomes were analyzed in patients with available follow-up data at the relevant time points. No missing values were imputed.

Primary endpoints

At 6 months postoperatively, the rates of IUC displacement/loss were 2.22% (2/90) in the GyneFix IUD + LNG-IUS group, 10.00% (9/90) in the ring IUD + LNG-IUS group and 18.89% (17/90) in the LNG-IUS-alone group, with statistically significant differences between groups (χ^2=13.468, P<0.001). Pairwise comparisons revealed that the displacement rate in the GyneFix IUD + LNG-IUS group was significantly lower than that in the ring IUD + LNG-IUS group (χ^2=4.744, P=0.029) and the LNG-IUS-alone group (χ^2=13.240, P<0.001); however, no statistically significant difference was observed between the ring IUD + LNG-IUS group and the LNG-IUS-alone group (χ^2=2.877, P=0.090). Kaplan-Meier survival analysis demonstrated that the cumulative continuation rate in the GyneFix IUD + LNG-IUS group was significantly higher than in the other two groups (Log-rank χ^2=18.500, P<0.001), see Fig. 2.

Secondary endpoints

Improvement of symptoms and signs

Among patients who completed a 6-month follow-up (GyneFix IUD + LNG-IUS group n=82, ring IUD + LNG-IUS group n=79, LNG-IUS-alone group n=78), the VAS scores of all three groups showed significant decreases at 1, 3 and 6 months postoperatively compared to preoperative levels (all P<0.05). At 6 months postoperatively, the VAS scores in the GyneFix IUD + LNG-IUS group decreased to (2.17±0.97) points, the ring IUD + LNG-IUS group to (2.51±1.31) points and the LNG-IUS-alone group to (2.05±1.09) points, but no statistically significant differences were observed among the groups (F=2.235, P=0.122). At 6 months postoperatively, the PBAC scores of all three groups also showed significant decreases compared to preoperative levels (all P<0.05). The PBAC scores in the GyneFix IUD + LNG-IUS group were (98.55±46.94) points, the ring IUD + LNG-IUS group (97.09±54.28) points and the LNG-IUS-alone group (98.12±53.32) points, with no statistically significant differences among the groups (F=0.017, P=0.983). At 6 months postoperatively, the uterine volumes of all three groups showed slight reductions compared to preoperative levels. The uterine volumes in the GyneFix IUD + LNG-IUS group were (130.54±58.48) cm³, the ring IUD + LNG-IUS group (128.06±64.37) cm³ and the LNG-IUS-alone group (129.89±68.88) cm³. No statistically significant differences in reduction rates were observed among the groups (F=0.395, P=0.674). The postoperative uterine volumes of all three groups showed no statistically significant differences compared to preoperative levels (all P>0.05), as detailed in Table 2.

Changes in laboratory parameters

Among patients who completed a 6-month follow-up (GyneFix IUD + LNG-IUS group n=82, ring IUD + LNG-IUS group n=79, LNG-IUS-alone group n=78), the Hb levels of all three groups showed significant increases at 6 months postoperatively compared to baseline (all P<0.05). The Hb levels were (125.06±10.97) g/L in the GyneFix IUD + LNG-IUS group, (126.19±10.39) g/L in the ring IUD + LNG-IUS group and (125.83±11.18) g/L in the LNG-IUS-alone group. No statistically significant differences were observed in Hb levels or the improvement from baseline among the three groups (F=0.228, P=0.796). At 6 months postoperatively, the serum CA125 levels of all three groups showed significant decreases compared to baseline (all P<0.05). The CA125 levels decreased to (28.27±22.21) U/mL in the GyneFix IUD + LNG-IUS group, (27.06±21.67) U/mL in the ring IUD + LNG-IUS group and (27.37±19.52) U/mL in the LNG-IUS-alone group. No statistically significant differences were observed in the CA125 levels or the decrease from baseline among the three groups (F=0.072, P=0.931). See Table 3 for details.

Table 1: Comparison of baseline data among the three groups ($\bar{x}$±s/ n(%))

Metric	GyneFix IUD + LNG-IUS group (n=90)	Ring IUD + LNG-IUS group (n=90)	LNG-IUS-alone group(n=90)	F/χ^2	*P*
Age (years)	41.52 ±5.94	42.17 ± 6.08	42.14± 5.18	0.364	0.695
BMI (kg/m^2)	21.28±1.65	20.98 ±1.75	20.72 ± 1.53	2.572	0.078
Menstrual cycle (days)	29.43 ±3.83	28.51± 3.85	29.19 ±3.54	0.454	0.617
Menstrual period (days)	6.37 ±1.66	6.33 ± 1.78	6.64±1.42	0.334	0.656
gravidity	3.61 ±1.68	3.94±1.66	3.68±1.64	1.013	0.364
parity	1.73±0.68	1.80±0.71	1.73±0.76	0.259	0.772
Number of miscarriages	1.83±1.71	2.14±1.63	1.97±1.44	0.860	0.424
GnRH-a pretreatment history [n (%)]	6 (6.67)	8 (8.89)	5(5.56)	0.793	0.673
History of IUC descent/loss [n (%)]	6 (6.67)	9 (10.00)	7 (7.78)	0.693	0.707
Combined myoma/adenomyoma [n (%)]	32 (35.56)	34 (37.78)	29 (32.22)	0.617	0.734
Uterine cavity depth>9cm [n (%)]	28 (31.11)	31 (34.44)	27 (30.00)	0.444	0.801

Note: BMI: Body Mass Index; GnRH-a: Gonadotropin-Releasing Hormone Agonist; IUC: Intrauterine Device; VAS: Visual Analogue Scale; PBAC: Menstrual Blood Loss Chart; Hb: Hemoglobin.

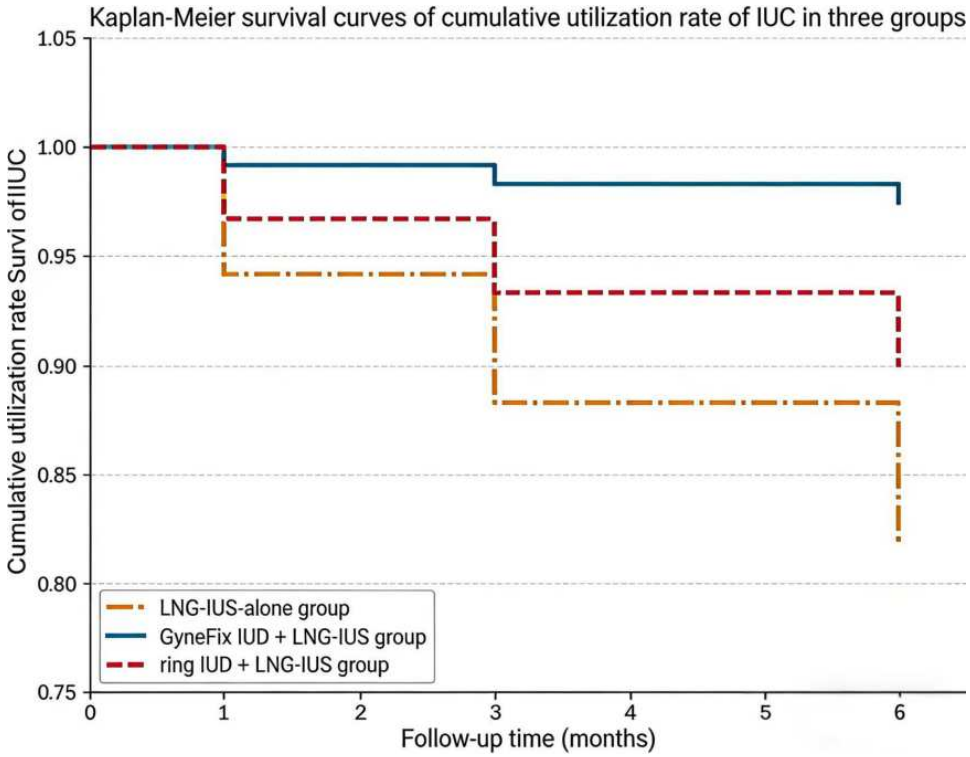

Fig. 2: Kaplan – meier curves of cumulative IUC continuation in the three groups

Comparison of adverse reaction incidence rates

In the safety dataset (GyneFix IUD + LNG-IUS group n=82, ring IUD + LNG-IUS group n=79, LNG-IUS-alone group n=78), the total incidence of adverse reactions within 6 months postoperatively was 41.46% (34/87), 44.30% (35/86) and 34.62% (27/85) in the three groups, respectively, with no statistically significant differences between groups (χ^2=1.620, *P*=0.3445). Among these, irregular vaginal bleeding was the most common adverse reaction, occurring in 31.71% (26/87), 29.11% (23/86) and 28.21% (22/85) of the groups, respectively, with no statistically significant differences between groups (χ^2=0.255, *P*=0.880). The incidence of low back pain was 8.54% (7/87), 12.66% (10/86) and 6.41% (5/85) in the three groups, respectively, with no statistically significant differences between groups (χ^2=1.900, *P*=0.387). The rate of symptom-driven removal was 1.15% (1/87), 2.33% (2/86) and 0.00% (0/85) in the three groups, respectively, with no statistically significant differences between groups (χ^2=2.031, *P*=0.362). There were no statistically significant differences in the incidence of pelvic inflammatory disease, ovarian cysts, breast tenderness, acne, or significant weight gain among the three groups (all *P*>0.05).

Table 2: Improvement of preoperative and postoperative symptoms and signs in the three patient groups

Group	n	VAS (component)			PBAC score (points)		
		Preoperative	3 months postoperatively	6 months postoperatively	Preoperative	3 months postoperatively	6 months postoperatively
GyneFix IUD + LNG-IUS group	82	6.78±1.62	4.61±1.94	2.17±0.97	165.62±70.82	136.61±62.80	98.55±46.94
ring IUD + LNG-IUS group	79	6.48±1.75	4.00±2.02	2.51±1.31	168.03±80.94	137.08±68.61	97.09±54.28
Monocyclic group	78	6.90±1.41	4.85±1.86	2.05±1.09	164.64±84.79	135.69±72.19	98.12±53.32
F		1.418	1.887	2.235	0.038	0.008	0.017
P		0.244	0.219	0.122	0.962	0.992	0.983

Table 2: (continued)

Group	n	Uterine volume (cm^3)		
		Preoperative	3 months postoperatively	6 months postoperatively
GyneFix IUD + LNG-IUS group	82	141.98±70.33	136.39±63.94	130.54±58.48
ring IUD + LNG-IUS group	79	139.29± 67.98	134.04± 65.74	128.06± 64.37
monocyclic group	78	135.16± 60.83	127.59± 57.94	123.30± 54.93
F		0.188	0.420	0.395
P		0.828	0.657	0.674

Table 3: Changes in laboratory parameters before and after surgery in the three patient groups.

Group	n	Hb (g/L)			CA125 (U/mL)		
		Preoperative	3 months postoperatively	6 months postoperatively	Preoperative	3 months postoperatively	6 months postoperatively
GyneFix IUD + LNG-IUS group	82	111.50± 21.03	116.30± 15.91	125.06± 10.97	61.78± 41.20	43.89± 30.81	28.27± 22.21
ring IUD + LNG-IUS group	79	112.66± 20.83	118.52± 14.00	126.19± 10.39	59.85± 39.22	41.60± 33.66	27.06± 21.67
monocyclic group	78	113.83± 19.50	119.69± 14.60	125.83± 11.18	60.15± 37.68	42.52± 26.55	27.37± 19.52
F		0.260	1.075	0.228	0.056	0.115	0.072
P		0.772	0.343	0.796	0.945	0.891	0.931

Treatment acceptance

A questionnaire survey conducted 6 months postoperatively among patients who completed follow-up showed that 95.12% (78/82) of patients in the Giman double-loop group indicated they were "willing" or "very willing" to choose this treatment method again, which was significantly higher than the 77.22% (61/79) in the ring IUD + LNG-IUS group group and the 88.46% (69/78) in the LNG-IUS-alone group (χ^2=9.731, *P*=0.008). In terms of recommendation willingness, 90.24% (74/82) of patients in the Giman double-loop group expressed a "willing" or "very willing" intention to recommend the treatment to others, also significantly higher than the 77.22% (61/79) in the ring IUD + LNG-IUS group and the 76.92% (60/78) in the LNG-IUS-alone group (χ^2=6.226, *P*=0.044).

Subgroup analysis based on uterine cavity depth in 262 cases

Subgroup analysis was performed with a uterine cavity depth of 9cm as the boundary. Among patients with a uterine depth>9 cm, the descent rate in the GyneFix IUD + LNG-IUS group (3.57%,1/28) was significantly lower than that in the Yuannan double-loop group (29.03%,9/31) and the LNG-IUS-alone group (40.74%,11/27) (χ^2=10.849, *P*=0.004). In patients with a uterine depth ≤9 cm, the descent rates in the three groups were 1/56(1.85),0/57 (0.00)

and 6/63 (9.52), respectively, with the lowest rates observed in the GyneFix IUD + LNG-IUS group and Yuannan double-loop groups (χ^2=8.215, P=0.016). Interaction analysis revealed no significant effect of uterine cavity depth on the descent reduction effect of the GyneFix IUD + LNG-IUS group (P for interaction=0.321), as shown in Table 4.

DISCUSSION

Overall significance of the study and main findings

As one of the most common benign gynecological conditions, AM has long been a focus of gynecological practice because of its substantial impact on the quality of life of women of reproductive age, particularly in terms of severe dysmenorrhea, menorrhagia and infertility (Moawad G *et al.*, 2023). At present, the main conservative treatments for AM include oral hormonal therapy and insertion of the LNG-IUS. Among these options, LNG-IUS is widely used in clinical practice as a first-line treatment because of its strong local efficacy and long-term therapeutic effect (Selntigia A *et al*, 2024). However, in patients with AM, especially those with enlarged uteri, the use of LNG-IUS is associated with a relatively high risk of displacement or expulsion, with reported rates ranging from 20% to 37.5% (Lin Y *et al.*, 2025). This problem has consistently limited its therapeutic effectiveness and reduced the number of patients who are suitable for this treatment (Zheng *et al.*, 2023). Therefore, this study prospectively and randomly compared GyneFix IUD + LNG-IUS with two other commonly used conservative treatment strategies, namely ring IUD + LNG-IUS and LNG-IUS alone, in patients with AM with different uterine cavity depths, while evaluating their efficacy and safety.

The results of this study supported our original hypothesis. In terms of device stability, the GyneFix IUD + LNG-IUS group showed superior performance compared with the other two groups. At 6 months postoperatively, the proportion of device displacement/expulsion in the GyneFix IUD + LNG-IUS group was the lowest, at only 2.22%, which was significantly lower than that in the ring IUD + LNG-IUS group (10.00%) and the LNG-IUS-alone group (18.89%). These findings suggest that the unique structural characteristics of the GyneFix IUD are a key factor underlying this advantage. Its anchoring knot can be embedded into the uterine fundal myometrium, thereby providing strong mechanical stability. This mechanism may resist uterine smooth muscle contraction during menstruation and the downward force generated by the cervical canal, helping the LNG-IUS remain in its optimal position within the uterine cavity (WEI Lan *et al.*, 2024). Subgroup analysis further showed that this stability advantage was particularly evident in patients with a uterine cavity depth >9 cm. Therefore, this strategy may represent an especially suitable treatment option for patients with uterine enlargement complicated by adenomyosis.

Symptom improvement and comparative efficacy

In addition, although all three groups showed significant improvement in subjective indicators such as pain relief and reduced menstrual bleeding, the between-group differences were not statistically significant (P>0.05). This suggests that as long as LNG-IUS can remain stably positioned and exert its physiological effects, definite clinical benefits can be achieved. The therapeutic benefit is primarily attributable to the local progestogenic effect of LNG-IUS itself (Fang F *et al*., 2021). The GyneFix IUD was not intended to enhance the pharmacological effect of LNG-IUS, but rather to ensure stable positioning of the device and to prevent treatment interruption caused by displacement or expulsion. Therefore, its main clinical advantage lies in improved device retention rather than superior symptom relief (Yingying L *et al*., 2023).

Comparison of fixation strategies and possible mechanism

In this study, the ring IUD + LNG-IUS strategy was also designed to provide physical support and thereby reduce device displacement. However, the expected stabilizing effect was limited, particularly in patients with deeper uterine cavities. This finding indicates that simple mechanical support may not fundamentally solve the problem of LNG-IUS instability in AM. The results of this study therefore provide direct evidence regarding the relative advantages and disadvantages of different fixation methods. Compared with LNG-IUS alone, the ring IUD + LNG-IUS strategy may reduce downward displacement to some extent, but the effect remains limited, especially in patients with a uterine cavity depth >9 cm, in whom the risk of expulsion remained relatively high. This suggests that passive support alone is insufficient to overcome the physiological and anatomical challenges associated with adenomyosis, such as uterine enlargement and abnormal uterine contractions. In contrast, the GyneFix IUD + LNG-IUS strategy is based on a fundamentally different anchoring principle, achieving mechanical fixation by actively implanting the anchoring knot of the GyneFix IUD into the fundal myometrium. The markedly lower displacement/expulsion rate in this group strongly supports the view that anchoring-based fixation is superior to passive support in maintaining device stability (Yingying L *et al.*, 2023). Therefore, for patients at high risk of expulsion, such as those with marked uterine enlargement, GyneFix IUD + LNG-IUS may provide a more reliable and durable therapeutic option.

Safety and tolerability

The incidence of adverse events in the GyneFix IUD + LNG-IUS group and its subgroups did not show a significant increase compared with the other two groups (P>0.05). There were no statistically significant differences among the three groups in the overall adverse event rate, the incidence of irregular vaginal bleeding, low back pain, or the rate of device removal for symptomatic reasons (P>0.05).

Table 4: Subgroup analysis based on uterine cavity depth for IUC displacement at 6 months postoperatively [n (%)]

Group	Uterine depth> 9 cm (n=86)	Uterine depth ⩽ 9 cm (n=176)	χ^2	*P*
GyneFix IUD + LNG-IUS group	1/28 (3.57)	1/56(1.85)	0.229	0.632
ring IUD + LNG-IUS group	9/31 (29.03)	0/57 (0.00)	21.909	<0.001
monocyclic group	11/27 (40.74)	6/63 (9.52)	21.812	<0.001
χ^2	10.849	8.215		
P	0.004	0.016		

These findings suggest that the use of GyneFix IUD in combination with LNG-IUS did not introduce additional short-term safety concerns in clinical practice. The main component of GyneFix IUD is an indomethacin-containing silicone rubber material. Indomethacin has anti-inflammatory and analgesic effects and inhibits prostaglandin synthesis in vivo, thereby reducing local inflammatory responses after endometrial injury and alleviating pain (Chen L *et al.*, 2024). This may be consistent with the absence of statistically significant differences in bleeding-related adverse reactions between GyneFix IUD + LNG-IUS and the other two treatment strategies in this study. In addition, because of its frameless, flexible and freely deformable design, GyneFix IUD may exert less mechanical irritation on the surrounding tissues, which may help explain the relatively low incidence of low back pain observed in this group (Ren J *et al.*, 2023).

Patient acceptance and clinical implications

The high stability of the device was also reflected in better patient-reported outcomes. The GyneFix IUD + LNG-IUS group showed higher treatment acceptability and a greater willingness to recommend the treatment than the other two groups. This finding reflects the fact that, in clinical practice, patients value not only therapeutic efficacy but also a smooth and reliable treatment process. A stable device position may reduce unnecessary outpatient visits, repeated procedures and the psychological burden associated with fear of device displacement or expulsion. The very low displacement rate may therefore improve treatment satisfaction and patient confidence.

Study limitations

This study has certain limitations. The one of important limitation is the 6-month follow-up duration. Although this period is sufficient to capture early device displacement/expulsion and short-term symptom changes, it is not adequate to assess long-term device stability, sustained efficacy, or recurrence of adenomyosis-related symptoms. This study was conducted in a single center and the applicability of the results should be carefully considered when generalizing the findings. Due to the inherent characteristics of the study design, some participants exhibited poor adherence and certain cases were excluded due to inclusion/exclusion criteria. These factors may potentially influence the final outcome analysis. Although a randomized controlled trial method was employed to control for certain unbalanced factors affecting the outcomes and standardized surgical procedures were implemented between the two groups to minimize human error, a certain degree of human bias still existed throughout the experiment. A further limitation is that the ultrasound physicians were not blinded because the implanted device type was visible on imaging, which may have introduced potential detection bias. However, this risk was mitigated by the use of standardized ultrasound protocols, predefined objective diagnostic criteria, independent blinded outcome assessors and blinded statistical analysis. In addition, some missing follow-up data were inevitable in this prospective study. However, no data imputation was applied and sensitivity analyses for the primary endpoint showed results consistent with the main analysis, supporting the robustness of the study conclusions.

This study was a prospective randomized controlled trial; however, formal clinical trial registration was not completed before patient enrollment. This should be considered a methodological limitation affecting transparency, although the study protocol, eligibility criteria, outcomes and analysis procedures were predefined and consistently implemented within the research team.

CONCLUSION

In summary, for patients with adenomyosis, the core advantage of the GyneFix IUD + LNG-IUS group lies in its exceptional device stability. This protocol, through its unique fundal myometrial anchoring technique, significantly reduces the risk of early displacement and expulsion of the IUD, a benefit particularly evident in patients with deeper uterine cavities. This fundamentally addresses the key clinical challenge affecting the sustained efficacy of LNG-IUS. Our study demonstrates that all three LNG-IUS-containing protocols effectively alleviate dysmenorrhea, reduce menstrual flow and improve anemia, with the therapeutic effects primarily attributed to the local pharmacological action of LNG. The GyneFix IUD + LNG-IUS ensures the continuous and stable positioning of the LNG-IUS, guaranteeing the continuity and reliability of the drug's efficacy rather than enhancing its pharmacological effects. Additionally, the 6-month data from this study indicate that the ring IUD + LNG-IUS and LNG-IUS-alone, which rely on the support principle, have

shown higher rates of early displacement. In contrast, the GyneFix IUD + LNG-IUS, based on the anchoring principle, provides long-term mechanical stability through its fixed anchor points (stable K-S distance) once successfully positioned, theoretically offering more effective prevention of long-term delayed expulsion. This protocol exhibits good safety without additional risks, ultimately achieving higher patient satisfaction. It provides a more stable and reliable alternative for the long-term management of adenomyosis, particularly for patients with a high risk of traditional LNG-IUS expulsion.

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Authors' contributions
Peipei LI, Tuo HE were responsible for the writing and data collection of this study and Jiwen PENG, Jie YANG were responsible for the conceptualization, communication and translation of this study.

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Data availability statement
The datasets generated during and/or analysed during the current study are available from the corresponding author on request.

Ethical approval
This study was reviewed and approved by the institutional ethics committee (KY-2023-200). This study was performed in adherence with the CONSORT guidelines. See supplementary file for the CONSORT checklist.

Conflict of interest
The authors declare that there is no conflict of interests.

Supplementary data
https://www.pjps.pk/uploads/2026/07/SUP1782911110.pdf

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