COMPARISON OF EFFICACY BETWEEN LEVONORGESTREL INTRAUTERINE SYSTEM AND DIENOGEST IN ADENOMYOSIS: A RANDOMIZED CLINICAL TRAIL

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INTRODUCTION

- Adenomyosis is a condition affecting women, primarily aged **40-50**, but it's increasingly seen in younger women too.

- This condition, which depends on **estrogen**, often causes symptoms like painful periods (**dysmenorrhea**), pain during sex (**dyspareunia**), **chronic pelvic pain**, and **heavy menstrual bleeding**.

- These symptoms can significantly disrupt daily life and lower the quality of life, making symptom relief a key part of managing adenomyosis.

MEDICAL MANAGEMENT OF ADENOMYOSIS

- The management of adenomyosis with medications is evolving. Here are some options:

- ✓ Levonorgestrel Intrauterine System (LNG-IUS)
- ✓ Gonadotropin-Releasing Hormone Agonist (GnRH-a)
- ✓ Combined Oral Contraceptives (COCs)
- ✓ Aromatase Inhibitors

- There are also some newer treatments showing promise:

✓ Dienogest (DNG)

✓ Selective Progesterone Receptor Modulators

✓ Dopamine Agonists

Levonorgestrel Intrauterine System (LNG-IUS):

- A long-acting reversible contraceptive approved for up to 8 years by the FDA.
- Works by **downregulating estrogen receptors**, causing **endometrial atrophy**, and **lowering prostaglandin production**, which helps in reducing pain and bleeding.
- More effective in reducing pain and heavy menstrual bleeding compared to combined oral contraceptives (COCs).
- Often used after surgical procedures to prevent recurrence.

Dienogest (DNG):

- An oral synthetic progestin with strong affinity to progesterone receptors.
- Works by **preventing ovulation**, **reducing estrogen levels slightly**, and **preventing blood vessel growth.**
- Shown to be effective in reducing pain and heavy menstrual bleeding in adenomyosis, possibly more so than COCs and GnRH agonists.
- Lacks long-term safety and efficacy data compared to other treatments.

Comparison of treatments

- Earlier studies on treatments for adenomyosis focused on objective outcomes like uterine size and blood flow, neglecting subjective improvements such as pain reduction, menstrual changes, and patient satisfaction.

- Both the Levonorgestrel Intrauterine System (LNG-IUS) and Dienogest (DNG) effectively reduce pain and heavy menstrual bleeding (HMB), but neither is officially approved for adenomyosis.

- Strong evidence from randomized clinical trials (RCTs) comparing their efficacy is lacking.

- This study is the first well-designed RCT to compare these treatments for adenomyosis with pelvic pain and/or HMB.

MATERIALS AND METHOD

- This study was a **single-center**, **open-label**, **parallel** randomized controlled trial (RCT) conducted at the All India Institute of Medical Sciences in Bhubaneswar, India.
- The trial was approved by the Institute Ethics Committee.
- Participant recruitment began on June 1, 2020, and ended on August 29, 2021.
- Data analysis was completed by November 30, 2021.
- Trial was prospectively registered at the clinical trial registry – India (CTRI) vide CTRI number CTRI/2020/05/025186.

Study Participants:

- The study included women over 20 years old who experienced **pelvic pain** (dysmenorrhea or chronic pelvic pain) **with or without uterine bleeding.**

- They were diagnosed with adenomyosis through two-dimensional ultrasonography and color Doppler.

- Diagnosis of adenomyosis was based on the **Morphological Uterus Sonographic Assessment** (**MUSA**) criteria, which includes:

1. Asymmetrical thickening of myometrial wall
2. Myometrial cysts
3. Hyperechoic islands
4. Fan-shaped shadowing
5. Echogenic sub-endometrial lines and buds
6. Translesional vascularity
7. Irregular junctional zone
8. Interrupted junctional zone

- Adenomyosis was diagnosed when **any two** of the above-mentioned features were found to be present.

- In cases of inconclusive diagnosis, a magnetic resonance imaging (MRI) of the pelvis was performed.

Inclusion Criteria:

- Women over 20 years old with pelvic pain diagnosed with adenomyosis by imaging.

Exclusion Criteria:

- Women with ovarian endometrioma or uterine fibroids.
- Those planned for hysterectomy or other treatments.
- Women wishing to become pregnant.
- Those with contraindications to LNG-IUS or DNG.
- Women with hemoglobin levels below 8 g/dL (treated for anemia before inclusion).

Baseline Measures:

- Participants provided written informed consent and were assessed for **pelvic pain**(Dysmenorrhea, Chronic pelvic pain) severity using the **Visual Analog Scale (VAS),** where 0 indicates no pain and 10 indicates intolerable pain.

- **Quality of life (QOL)** was assessed using the **WHO-QOL BREF** questionnaire, available in English or the patient's preferred language.

- This questionnaire has **26** questions in **four** domains: physical health, psychological health, social relationships, and environment.

- Participants answered the questionnaire based on their experiences over the past two weeks.

- Each domain's score was calculated and converted to a 0-100 scale as per the questionnaire manual.

- The overall QOL score was the sum of all domain scores. Higher scores indicate better quality of life.

Randomization and Treatment

- Participants were allocated to one of two groups after randomization using a **computer-generated block scheme (Block size=10)** and allocated using **sealed opaque envelope** method.

- Preparation and sorting of the serially numbered envelopes were performed by an investigator who did not participate in evaluating patients either before recruitment or in the follow-up stage.

- **LNG-IUS Group:** Received the LNG-IUS (Mirena 52mg) device.

- **DNG Group:** Took 2mg of DNG orally once daily for 12 weeks, starting between the 2nd and 5th day of their menstrual cycle.

Follow-Up and Outcome Measures

- Participants had a follow-up visit **12 weeks** later to assess outcomes.

- Compliance with Dienogest (DNG) was checked by asking participants to show their empty medicine packets.

- Pelvic pain (dysmenorrhea and chronic pelvic pain) and quality of life (QOL) were assessed the same way as before the intervention.

- Menstrual blood loss (MBL) was evaluated subjectively, asking if it was light, heavy, or normal, following the International Federation of Gynecology and Obstetrics guidelines.

- Participants were also asked about any side effects like hot flushes, breast tenderness, vaginal spotting, amenorrhea, or other unusual symptoms.

- The **primary outcome** was the change in adenomyosis-related pelvic pain (dysmenorrhea or chronic pelvic pain) from before treatment to 12 weeks after treatment, measured by the Visual Analog Scale (VAS).

- **Secondary outcomes** included changes in menstrual patterns, changes in quality of life (QOL), and any reported side effects.

Sample Size and Data Analysis

- The sample size calculation was based on the primary outcome (improvement in pain as indicated by VAS score after treatment).

- Using a two-sided chi-square test with an α of 0.05, the total sample size was calculated to be 106 patients in the 2 groups (i.e. 53 in each arm) with 80% power to detect a 30% difference in VAS score between LNG-IUS and DNG.

- Assuming a dropout rate of 10%, the study was supposed to recruit 120 participants (i.e. 60 in each arm)

- Data analysis used **IBM-SPSS** version 23(Statistical Package for the Social Sciences; International Business Machines Corporation, New York, United States):

- **Continuous Variables:** Mean and standard deviation (e.g., age, VAS, QoL scores).

- **Categorical Variables:** Percentages (e.g., presence of symptoms, bleeding assessment).

- Paired t-tests compared pre- and post-treatment measures within groups, while unpaired t-tests compared between groups.

- For dichotomous variables, chi-square was used to estimate the significance value.

- p-value of <0.05 was considered statistically significant.

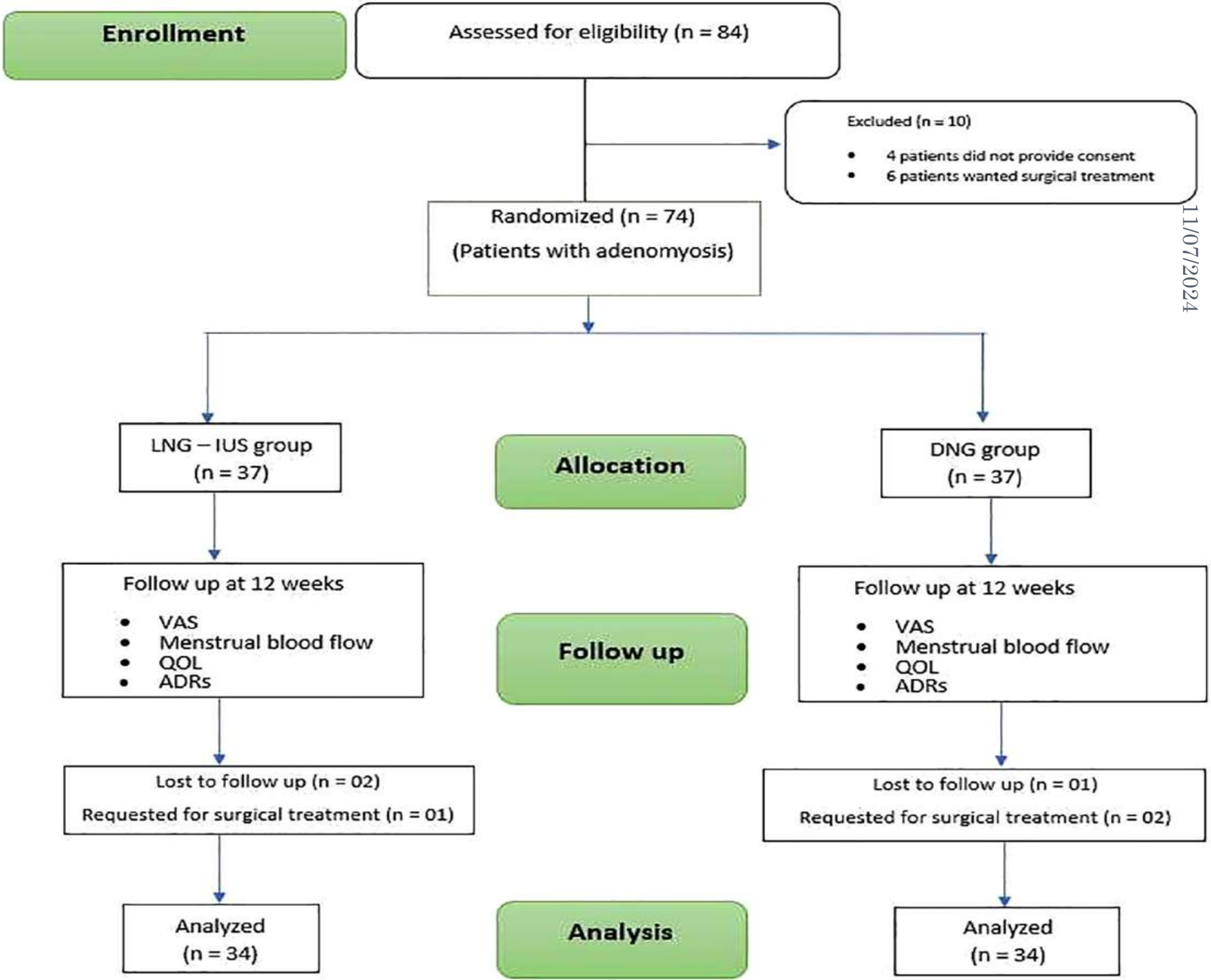
RESULTS

- **Initial Assessment**: Initially, **84** eligible women were assessed to participate in the study.

- **Recruitment**: Eventually, **74** women were recruited, with 37 assigned to each treatment group (LNG-IUS and DNG).

- **Exclusions**: Ten patients were excluded from the study:

- 4 patients did not agree to participate.
- 6 patients opted for surgical treatment instead of participating in the study.


Enrollment
Assessed for eligibility (n = 84)
Excluded (n = 10)
4 patients did not provide consent
6 patients wanted surgical treatment
Randomized (n = 74)
(Patients with adenomyosis)
LNG – IUS group
(n = 37)
Allocation
DNG group
(n = 37)
Follow up at 12 weeks
VAS
Menstrual blood flow
QOL
ADRs
Follow up
Follow up at 12 weeks
VAS
Menstrual blood flow
QOL
ADRs
Lost to follow up (n = 02)
Requested for surgical treatment (n = 01)
Lost to follow up (n = 01)
Requested for surgical treatment (n = 02)
Analyzed
(n = 34)
Analysis
Analyzed
(n = 34)

- **Analysis**: The final analysis included 34 patients in each group (totaling 68 patients analyzed), following the study protocol.

- **Baseline Characteristics**: Both groups were similar in most baseline characteristics, except for the **prevalence of Heavy Menstrual Bleeding (HMB).**

- **Statistical Finding**: The prevalence of HMB was significantly higher in the LNG-IUS group compared to the DNG group ($p = 0.022$).

- **MRI Pelvis**: MRI pelvis scans were done for a few patients in both the LNG-IUS and DNG groups. This happened because their ultrasound (USG) results showed uncertain findings.

- **Minor Discrepancies**: The MRI scans showed minor differences compared to the ultrasound findings. Despite these differences, the MRI results were used to make the final diagnosis.

- **Menstrual Bleeding**: A significantly higher number of patients in the LNG-IUS group reported lighter menstrual bleeding compared to the DNG group (90% vs. 77.2%, p = 0.006).

- **Pain Improvement**: Both the LNG-IUS and DNG groups showed significantly lower pain scores measured by VAS (Visual Analog Scale) after treatment compared to before:

- LNG-IUS: Pain scores reduced from 6.41 to 3.41 ($p < 0.001$).
- DNG: Pain scores reduced from 6.41 to 3.12 ($p < 0.001$).

- However, the difference in pain reduction between the two groups was not statistically significant (LNG-IUS: 3.00 vs. DNG: 3.29, $p = 0.389$).

- **Quality of Life (QOL):** Overall, both treatment groups showed significant improvements in QOL after treatment:

- LNG-IUS: Significant improvements in most QOL domains except social relationships (p = 0.062).

- DNG: Significant improvements in overall QOL and the other 4 domain of QOL.

- The overall QOL and environment domain improvement of QOL was significant in the DNG group compared to LNG-IUS group.

- A common adverse event of both LNG-IUS and DNG is vaginal spotting.

DISCUSSION

- In conclusion, while both LNG-IUS and DNG are effective for treating adenomyosis symptoms, LNG-IUS may be preferred for reducing menstrual bleeding, while DNG could be considered for improving overall quality of life.

- Our study showed that both groups experienced significantly less pain after treatment.

- While LNG-IUS has been well-studied for managing pain and bleeding in adenomyosis, there's limited research on how effective DNG is for these symptoms.

Table 1. Baseline characteristics.

Baseline characteristics	LNG-IUS group ($n=34$)	DNG group ($n=34$)	p Value
Age (years)[a]	40.06 ± 6.95	40.97 ± 6.78	0.591
BMI (kg/m^2)[a]	27.53 ± 3.93	27.85 ± 3.79	0.337
Parity[a]	2.00 ± 0.88	1.85 ± 0.92	0.627
Number of living children[a]	1.91 ± 0.83	1.82 ± 0.90	0.761
Number of abortion[a]	0.47 ± 1.26	0.79 ± 1.03	0.075
Previous mode of delivery			0.583
• Vaginal delivery	23 (67.6)	24 (70.5)	
• Cesarean delivery	08 (23.5)	09 (34.6)	
Duration from last pregnancy (years)[a]	13.24 ± 7.28	14.38 ± 6.21	0.652
Dysmenorrhea	30 (88.2)	32 (94.1)	0.393
CPP	7 (20.5)	7 (20.5)	1.000
HMB	30 (88.2)	22 (64.7)	0.022
VAS[a]	6.41 ± 1.07	6.41 ± 0.95	1.000
Hb[a]	10.38 ± 1.43	10.71 ± 1.36	0.644

[a]Data represented as mean ± standard deviation, rest as frequency (percentage).
BMI, body mass index; CPP, chronic pelvic pain; DNG, dienogest; Hb, hemoglobin; HMB, heavy menstrual bleeding; LNG-IUS, levonorgestrel intrauterine system; VAS, visual analog scale.

Table 2. Change in VAS and QOL score.

Outcomes	LNG-IUS group ($n=34$)			DNG group ($n=34$)			Intergroup comparison
	Baseline	After 12 weeks	p Value	Baseline	After 12 weeks	p Value	p Value
VAS	6.41 ± 1.07	3.41 ± 1.04	<0.001	6.41 ± 0.95	3.12 ± 1.40	<0.001	0.389
QOL overall	231 ± 50.14	259.76 ± 50.5	<0.001	240.97 ± 61.02	289.24 ± 49.23	<0.001	0.040
QOL domain 1 (physical health)	59.97 ± 16.12	67.09 ± 17.78	<0.001	54.35 ± 19.67	67.94 ± 13.83	<0.001	0.064
QOL domain 2 (psychological health)	55.79 ± 12.67	66.06 ± 11.60	<0.001	59.26 ± 15.67	71.15 ± 15.37	<0.001	0.601
QOL domain 3 (social relationship)	56.29 ± 20.57	62.68 ± 21.29	0.062	65.26 ± 19.77	75.97 ± 13.63	<0.001	0.303
QOL domain 4 (environment)	58.94 ± 14.49	63.94 ± 12.02	<0.001	62.09 ± 19.81	74.18 ± 16.41	<0.001	0.033

Data represented as mean ± standard deviation.
QOL, quality of life; VAS, visual analog scale.

Table 3. Adverse drug reactions in both groups.

Adverse drug reactions	LNG-IUS group ($n=34$)	DNG group ($n=34$)
Vaginal spotting	8 (23.5)	13 (38.2)
Amenorrhea	7 (20.5)	9 (26.4)
Breast tenderness	3 (0.08)	4 (0.11)
Hot flushes	0 (0)	3 (0.08)

Data represented as frequency (percentage).

- Ota et al. found that after 3 months, DNG reduced VAS pain scores more than LNG-IUS.
- Osuga et al. followed patients for 16 weeks, showing DNG reduced pain similar to placebo.
- Hirata et al. observed significant reductions in pain symptoms with DNG over 24 weeks.
- Neriishi et al. reported DNG's long-term use (>80 months) reduced dysmenorrhea VAS scores significantly.
- Hassanin et al. found DNG significantly reduced VAS pain scores more than COCs.

- Fawzy et al. concluded DNG and triptorelin acetate equally reduced VAS scores for dyspareunia and CPP.
- Matsushima et al. showed DNG improved symptoms like dysmenorrhea and CPP after GnRH-a therapy.
- Ota et al. found DNG reduced VAS scores significantly post-microwave endometrial ablation in adenomyosis.
- These studies support DNG's effectiveness in reducing painful symptoms of adenomyosis compared to other treatments like COCs and triptorelin acetate.
- In our study, more patients using LNG-IUS experienced a decrease in menstrual bleeding compared to those using DNG.

- Studies support that:

- LNG-IUS effectively reduces abnormal uterine bleeding in adenomyosis patients after 6 months.

- LNG-IUS is more effective in reducing menstrual bleeding compared to low-dose oral contraceptive pills (OCPs) in clinical trials.

- DNG has shown a significant decrease in uterine bleeding days after 12 months compared to LNG-IUS in controlled trials.

- This study used patients' subjective assessment of menstrual bleeding volume, a method not commonly used in previous research on adenomyosis.

- Previous studies typically used objective methods like the Pictorial Blood Assessment Chart, the number of sanitary pads used ,maintaining a menstrual diary, or changes in Hb level.

- Our approach considers all aspects of quality of life affected by menstrual bleeding, which we believe is superior.

- Both treatment groups showed significant overall improvement in quality of life after 12 weeks.

- Ozdegirmenci et al. found that the LNG-IUS treatment is at least as effective as a hysterectomy in improving overall quality of life (QOL) and is even better for psychological and social aspects after 12 weeks of treatment.

- The improvement in QOL in the DNG group is also supported by a placebo-controlled study by Osuga et al., which showed significant improvement in QOL for 35 patients with adenomyosis, specifically in terms of pain symptoms.

- This suggests that DNG could be a better progestin for overall QOL improvement, including physical health, psychological well-being, social relationships, and environmental factors.

- The main reason for stopping DNG treatment is irregular uterine bleeding, which can lead to severe anemia.

- Risk factors for this bleeding include young age, pre-existing anemia before starting DNG and changes in estradiol levels during treatment.

- In our study, we didn't observe severe anemia caused by uterine bleeding in the DNG group because we treated severe anemia in two patients before they started DNG.

Our study's strengths include:

- It was a randomized controlled trial (RCT), which is a robust study design.
- It's the first prospective RCT comparing LNG-IUS and DNG for adenomyosis treatment.
- We used ultrasound (USG) based on MUSA guidelines for adenomyosis diagnosis, reducing variability in results.
- Patient-assessed menstrual bleeding provided comprehensive insight into how bleeding affects quality of life (QOL).

- We used the WHO-QOL BREF questionnaire in both English and the local language, minimizing communication bias.

- These strengths enhance the reliability and applicability of our study findings in comparing LNG-IUS and DNG effectiveness in adenomyosis treatment.

Our study had some limitations:

- **Limited Number of Participants**: The small participant size reduces how broadly we can apply our findings.
- **Short Follow-up Period**: We only followed patients for 12 weeks, so we couldn't assess long-term effectiveness or safety.
- **Secondary Outcome Measures**: We didn't measure uterine volume or uterine artery blood flow due to the short follow-up.
- **QOL Questionnaire**: The WHO-QOL BREF used isn't specific to adenomyosis, which lacks a validated disease-specific QOL measure, unlike conditions like uterine fibroids or endometriosis.

CONCLUSION

- Both LNG-IUS and DNG effectively reduce painful symptoms like dysmenorrhea and chronic pelvic pain (CPP).
- LNG-IUS is more effective than DNG in reducing menstrual bleeding (MBL).
- DNG shows better improvement in quality of life (QOL).
- DNG can be a safe and effective alternative to LNG-IUS for treating adenomyosis.
- Future multicenter randomized controlled trials with larger participant groups and longer follow-up periods are needed to better compare the efficacy and safety of DNG and LNG-IUS in adenomyosis treatment.

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- **Competing interests**

- The authors declare that there is no conflict of interest.

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Critical Appraisal

Title

“Comparison of efficacy between levonorgestrel intrauterine system and dienogest in adenomyosis: a randomized clinical trial”

Suggested Title

“Comparison of efficacy and safety between levonorgestrel intrauterine system and dienogest in adenomyosis: a randomized clinical trial”

Critical Appraisal based on Consort Checklist

Sr no.	Title	Justified	Not Justified	Comments
1.	Title & Abstract	✓		•Study can be identified as randomized trail from the title •Structured summary of trial design, methods, results, and conclusions are given
Introduction				
2a	Background	✓		•Study Explain the scientific background and rationale for the trial
2b	Objectives	✓		•Specific objectives are given

Methods

Trial design

Sr no.	Title	Justified	Not Justified	Comments
3a	Description of trial design (such as parallel, factorial) including allocation ratio		✓	• Trial design is mentioned(parallel) • Allocation ratio is not mentioned
3b	Important changes to methods after trial commencement (such as eligibility criteria)	✓		• No changes in methods after trial commencement

Participants

Sr no.	Title	Justified	Not Justified	Comments
4a	Eligibility criteria for participants	✓		Inclusion and exclusion criteria are mentioned
4b	Settings & locations where the data were collected	✓		Single centred study at AIIMS Bhubneswar
Intervention				
5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	✓		▪**LNG-IUS Group:** Received the LNG-IUS (Mirena 52mg) device. ▪**DNG Group:** Took 2mg of DNG orally once daily for 12 weeks, starting between the 2nd and 5th day of their menstrual cycle

Outcomes & Sample size

Sr no	Title	Justified	Not Justified	Comments
6	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	✓		The **primary outcome** was the change in adenomyosis-related pelvic pain from before treatment to 12 weeks after treatment, measured by the Visual Analog Scale (VAS). ➢**Secondary outcomes:** included changes in menstrual patterns, changes in quality of life (QOL), and any reported side effects.
7a	How sample size was determined	✓		Using a two-sided chi-square test with an α of 0.05, the total sample size was calculated to be 120 patients with 10% dropout rate.(106)
7b	When applicable, explanation of any interim analyses and stopping guidelines	----	----	NA

Randomisation

Sr no.	Title	Justified	Not Justified	Comments
8a	Method used to generate the random allocation sequence	✓		Computer generated block randomization scheme
8b	Type of randomization		✓	Not mentioned
9	Mechanism used to implement the random allocation sequence	✓		Serially numbered sealed opaque envelopes.

Sr no	Title	Justified	Not Justified	Comments
10	Implementation		✓	Information regarding investigator who generated the random allocation sequence is given But the information regarding investigator who enrolled participants and who assigned intervention is not given
11	Blinding	✓		Open labeled study
12	Statistical methods	✓		Data analysis used **IBM-SPSS** version 23(Statistical Package for the Social Sciences; International Business Machines Corporation, New York, United States) Paired t-tests compared pre- and post-treatment measures within groups, while unpaired t-tests compared between groups.

Results

Sr no	Title	Justified	Not Justified	Comments
13	Participants flow	✓		Information regarding numbers of participants who were randomly assigned, received treatment and analysed for the primary outcome is given
14	Recruitment	✓		Dates defining the periods of recruitment is mentioned from 1 june 2020 to 29 August 2021 but given in methods.
15	Baseline data	✓		Baseline data is given but in discussion part.

Sr no.	Title	Justified	Not Justified	Comments
16	Outcomes & estimation		✓	The study has presented the results for each outcome, including effect sizes, but it is missing information regarding confidence intervals.
		Discussion		
17	Limitations	✓		Trial limitations are mentioned
18	Generalisability	✓		The small participant size reduces the generalisability of findings.
19	Interpretation	✓		Study has provided an interpretation of the results in the context of existing evidence, considering both benefits and harms.

Other Information

Sr no.	Title	Justified	Not Justified	Comments
20	Registration	✓		Registration number and name of trial registry is mentioned
21	Protocol	✓		Study protocol will be shared on request.
22	Funding	✓		The authors received no financial support for the research, authorship, or publication of this article.


Thank You!