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Original Research Article

Fertility outcome following ovarian stimulation in infertile women having pretreatment with levonorgestrel releasing intrauterine system versus dienogest for symptomatic adenomyosis

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ABSTRACT

Background: Adenomyosis is an emerging enigmatic uterine disease that negatively impacts women's fertility. Conservative treatments, including medical management, offer hope to preserve future fertility but remain challenging, especially in low-resource settings. Since 2019, at our center, infertile women diagnosed with symptomatic adenomyosis have been pre-treated with either a Levonorgestrel-Releasing Intrauterine System (LNG-IUS) or Dienogest based on physician preference. Following symptomatic relief, ovarian stimulation protocols were applied to optimize the chances of natural conception without assisted reproductive technologies (ART). This study aimed to compare fertility outcomes following ovarian stimulation in infertile women with symptomatic adenomyosis who had been pre-treated with LNG-IUS versus Dienogest.
Methods: This quasi-experimental study was conducted at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from January 2024 to December 2024. Infertile women with previously diagnosed symptomatic adenomyosis, symptomatically relieved by LNG-IUS or Dienogest, were enrolled. Following enrolment, LNG-IUS devices were removed and Dienogest was discontinued. Participants were divided into two groups: Group A (pre-treated with LNG-IUS) and Group B (pre-treated with Dienogest) and both underwent ovarian stimulation using oral ovulogens.
Results: Both groups were comparable in baseline socio demographic, biochemical and biophysical criteria. Ovulation and pregnancy rate in each cycle were higher in LNG-IUS group than Dienogest group though this difference was not statistically significant ($p>0.05$).
Conclusions: Pre-treatment with LNG-IUS prior to ovarian stimulation may offer better fertility outcomes compared to Dienogest, though larger studies involving more cycles and multicenter collaboration are necessary to confirm these findings.

Keywords: Dienogest, Fertility outcome, Levonorgestrel intrauterine system, Ovarian stimulation, Symptomatic adenomyosis

INTRODUCTION

Adenomyosis is a frequent, estrogen-dependent, benign gynaecological disorder.[1] It is characterized by the presence of endometrial glands and stroma located deep into the myometrium, producing local or diffuse thickening and an enlarged uterus which can cause reproductive failure in women of reproductive age.[2] Adenomyosis frequently occurs alongside other gynecological disorders such as endometriosis and leiomyoma.[3] Its reported prevalence ranges significantly from 5% to 70% depending on the diagnostic approach used, with an average prevalence estimated between 20% and 30%.[4] In a recent cross-sectional study on infertile women, adenomyosis prevalence was 24.4% in women at least 40 years old and 22% in women less than 40 years old. This percentage is increased to 38.2% in cases of recurrent pregnancy loss and to 34.7% in previous ART failure.[5] According to a meta-analysis, the prevalence of adenomyosis in a population of infertile women undergoing in IVF/ICSI varied from 6.9% to 34.3%.[6]

The main clinical manifestations of adenomyosis include progressive dysmenorrhea, menorrhagia, dyspareunia and infertility. Around 24% of infertile women of adenomyosis, suffer from recurrent implantation failures and recurrent miscarriages which severely impact the physical and mental state of patients and reduce the overall quality of life.[7]

Although adenomyosis is both common and often associated with severe symptoms, its exact pathogenesis is still a subject of debate.[8] Development of endometrial tissue from embryologically misplaced pluripotent Müllerian remnants and mechanical invagination of the endometrium into the myometrium are two of the most widely accepted theories.[9] In adenomyosis-associated infertility there are dysregulations of the myometrial architecture and function, chronic inflammation, presence of local oxygen and altered endometrial function, which cause implantation failure.[7] Here eutopic endometrium shows altered sex steroid hormone pathway, increased inflammatory markers and oxidative stress, reduced expression of implantation markers, lack of expression of adhesion molecules and altered function of the gene for embryonic development (HOXA 10 gene), causing an impairment of implantation.[3]

Currently, the non-invasive imaging techniques, including 2D and 3D transvaginal scan with color Doppler as well as MRI, allow the proper identification of the different phenotypes of adenomyosis (diffuse and/or focal) and differentiating it from leiomyomas.[6]

Until recently, hysterectomy has been the only definitive treatment in women who have completed child bearing.[10] Treatment of adenomyosis in subfertile patients is extremely challenging for practicing gynaecologist as preservation of the uterus for future childbearing is the aim and desire of all women.[11] With the continuous exploration a number of new drugs, treating concepts and uterus-sparing surgical treatment options have recently been developed for adenomyotic patients who have infertility or fertility intentions but lack specificity.[6]

Among the conservative treatment options oral dienogest and levonorgestrel-releasing intrauterine system (LNG-IUS) are proved to be effective at alleviating symptoms and improving the patient's quality of life.[12] It has been shown that GnRH agonists also help women achieve a better In Vitro Fertilization (IVF) outcome.[7] The use of preparatory treatment with GnRH-agonists increased the pregnancy rate from 5 to 12% per IVF attempt.[13]

Objective

The objective of this study was to compare the fertility outcome following ovarian stimulation in infertile women having pretreatment with levonorgestrel releasing intrauterine system (LNG-IUS) and Dienogest for symptomatic adenomyosis.

METHODS

This quasi-experimental study was conducted at the Department of Reproductive Endocrinology and Infertility, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from January to December 2024. A total of 32 infertile women aged 20–35 years with symptomatic adenomyosis who achieved symptomatic relief after six months of pretreatment with either the Levonorgestrel-Releasing Intrauterine System (LNG-IUS) or Dienogest were included. Participants were purposively selected and divided into two equal groups: Group A received LNG-IUS pretreatment and Group B received oral Dienogest 2 mg daily for six months. Inclusion criteria were a normozoospermia male partner, at least one patent fallopian tube and normal ovarian reserve (FSH≤12 mIU/ml, AMH≥1.2 ng/ml and AFC 6–16). Exclusion criteria included thyroid disorders, BMI<18.5 or >30 kg/m² and contraindications to ovulation induction medications.

Following pre-treatment, participants underwent a controlled ovulation induction protocol using Letrozole (7.5 mg/day from Day 2 to Day 6) followed by subcutaneous injections of FSH (75 IU on Days 5 and 7). Follicular growth and endometrial response were monitored by transvaginal ultrasonography (TVS) on Days 8 and 12. When at least one dominant follicle reached≥18 mm, an intramuscular HCG injection (5,000 IU) was administered to trigger ovulation. Timed intercourse was advised 36 hours post-HCG. Ovulation was confirmed by TVS based on follicular collapse and fluid in the pouch of Douglas and pregnancy was assessed biochemically using serum β-HCG and clinically by TVS to confirm the presence of a gestational sac. The protocol was repeated for up to three cycles or until pregnancy occurred.

Data were collected on sociodemographic characteristics, baseline hormonal and ultrasound findings and treatment outcomes. Statistical analysis was conducted using SPSS version 23. Descriptive statistics were presented as mean±SD or median (IQR) and comparisons between groups were performed using Student's t-test, Mann-Whitney U test or Chi-square test, as appropriate. A p-value<0.05 was considered statistically significant. Ethical approval was obtained from the IRB of BSMMU and written informed consent was secured from all participants.

RESULTS

Table 1 presents the demographic and socioeconomic characteristics of participants in Group A (LNG-IUS) and Group B (Dienogest), showing no statistically significant differences across all parameters. Age distribution, educational background, occupation, monthly income, type and duration of subfertility were comparable. Mean age was similar (30.81±3.14 vs. 31.18±3.03 years, p=0.72), as was mean income (34,375±9,105.85 vs. 31,625±15,244.12 taka, p=0.71). Most participants had secondary education and were housewives, while their husbands were mainly in service-based jobs. Primary subfertility was more common in Group B (43.8%) and secondary subfertility in Group A (81.3%), without significant difference (p=0.12). The duration of subfertility was also comparable between the groups (p=0.59).

Table 1: Baseline demographic characteristics of group A (Pre-treatment with LNG-IUS) and Group B (Pre-treatment with Dienogest).

Characteristics	Group A (n=16)		Group B (n=16)		P value
	(N)	(%)	(N)	(%)	
Age (in years)					
20-27	8	50.0	3	18.8	[a]0.06[ns]
28-35	8	50.0	13	81.3	
Mean±SD	30.81±3.14		31.18±3.03		[m]0.72[ns]
Median (IQR)	29.50 (28.25-34.75)		32 (30-34)		
Education					
Illiterate	0	0.0	1	6.3	
Primary	3	18.8	3	18.8	
SSC	5	31.3	5	31.3	[a]0.61[ns]
HSC	6	37.5	3	18.8	
Graduate	2	12.5	4	25.0	
Occupation					
Housewife	14	78.5	12	75.0	
Service	2	12.5	4	25.0	[f]0.65[ns]
Husbands' occupation					
Business	2	12.5	4	25.0	
Service	9	56.3	9	56.3	[a]0.14[ns]
Farmer	0	0.0	2	12.5	
Labour	5	31.3	1	6.3	
Monthly income (taka)					
10,000-39900	11	68.8	10	62.5	
40,000-79900	5	31.3	6	37.5	[a]0.71[ns]
Mean±SD	34375.00±9105.85		31625.00±15244.12		[c]0.71[ns]
Types of subfertility					
Primary	3	18.8	7	43.8	[a]0.12[ns]
Secondary	13	81.3	9	56.3	
Duration of subfertility					
Mean±SD	5.68±3.28		6.75±4.13		[m]0.59[ns]
Median (IQR)	5 (3.25-7)		5 (4-9.25)		

Data was presented as frequency and percentage over the columns. Mean±SD and Median presented over the rows. P value reached through, a=Chi-square test for categorical variables, m=Mann Whitney U-test for non-normally distributed continuous variables, ns=non-significant, c=Unpaired t-test for normally distributed continuous variables, f=Fisher exact test for categorical variables, where expected value was <5 in ≥20% cells.

Table 2: Baseline clinical and laboratory variables of group A (Pre-treatment with LNG-IUS) and Group B (Pre-treatment with Dienogest).

Clinical presentations	Group A (n=16)		Group B (n=16)		P value
	(N)	(%)	(N)	(%)	
Menstrual cycle					
Regular	13	81.3	14	87.5	[f]1.00[ns]
Irregular	3	18.8	2	12.5	
Amount of blood loss					
Low	2	12.5	0	0.0	[a]0.09[ns]
Average	10	62.5	15	93.8	
High	4	25.0	1	6.3	
VAS pain score					
Mean±SD	5.00±3.16		3.68±1.66		[m]0.42[ns]
Median (IQR)	4 (2-8.25)		4 (2.25-4.75)		
Hemoglobin					
Mean±SD	10.80±1.04		11.00±0.97		[c]0.59[ns]

Data presented as frequency and percentage over the columns. Mean±SD and Median presented over the rows. P-value reached through, a=Chi-square test for categorical variables, m=Mann Whitney U-test for non-normally distributed continuous variables, ns=non-significant, f=Fisher exact test for categorical variables, where expected value was <5 in ≥20% cells.

Table 3: Distribution of group A (Pre-treatment with LNG-IUS) and Group B (Pre-treatment with Dienogest) according to baseline D5 TVS findings.

D5 TVS findings	Group A (n=16)		Group B (n=16)		P value
	(N)	(%)	(N)	(%)	
Uterine volume					
Mean±SD	127.33±68.74		97.96±37.60		[m]0.07[ns]
Median (IQR)	128 (74.25-138.75)		98 (72.50-109)		
Endometrium thickness					
Mean±SD	4.70±0.50		4.85±0.79		[m]0.80[ns]
Median (IQR)	4.6 (4.27-5.17)		5 (4.05-5)		
AFC					
Mean±SD	8.81±1.16		9.68±2.21		[m]0.34[ns]
Median (IQR)	8 (8-9)		9 (8-10)		

Data presented as frequency and percentage over the columns. Mean±SD and Median presented over the rows. P-value reached through, a=Chi-square test for categorical variables, m=Mann Whitney U-test for non-normally distributed continuous variables, ns=non-significant, f=Fisher exact test for categorical variables, where expected value was <5 in ≥20% cells.

Table 2 shows the clinical characteristics of Group A and Group B reveal several similarities and differences. Most participants in both groups have regular menstrual cycles, with irregular cycles reported by a small proportion and this difference is also not significant (p=1.00). Regarding blood loss, low levels were reported only in Group A (12.5%), while average blood loss was more common in Group B (93.8%) than in Group A (62.5%). High blood loss was more frequent in Group A (25.0%) than in Group B (6.3%), though these differences were not statistically significant (p=0.09). In terms of VAS pain scores, Group A exhibited a slightly higher mean score (5.00±3.16) compared to Group B (3.68±1.66), with a wider interquartile range, though the difference was not significant (p=0.42). In terms of hemoglobin, Group A's mean was 10.80±1.04 and Group B mean was 11.00±0.97, with a p-value of 0.59, suggesting no significant difference.

The TVS findings between Group A and Group B were compared in terms of uterine volume, endometrial thickness and AFC. Regarding uterine volume, Group A had a larger mean volume (127.33±68.74 mL) compared to Group B (97.96±37.60 mL), with median values of 128 (IQR: 74.25–138.75) in Group A and 98 (IQR: 72.50–109) in Group B. The p-value of 0.07 suggests a trend toward a difference, though it is not statistically significant. For endometrial thickness, Group A had an average thickness of 4.70±0.50 mm, while Group B had 4.85±0.79 mm. The median values were 4.6 (IQR: 4.27–5.17) in Group A and 5.0 (IQR: 4.05–5.0) in Group B, with a p-value of 0.80, indicating no significant difference between the two groups. Lastly, for AFC (Antral Follicle Count), Group A had a mean count of 8.81±1.16, while Group B had 9.68 ± 2.21, with median values of 8 (IQR: 8–9) in Group A and 9 (IQR: 8–10) in Group B. The p-value of 0.34 shows no significant difference between the two groups in AFC (Table 3).

The study compared the number of growing follicles between Group A and Group B over three treatment cycles. In the first cycle, the mean±SD number of follicles was 4.68±1.19 in Group A and 5.06±1.38 in Group B, with median (IQR) values of 5 (4-5) and 5 (4.25-6), respectively. During the second cycle, the mean±SD was 4.78±1.25 for Group A and 5.42±1.28 for Group B, with median (IQR) values of 4.5 (4-6) and 5 (4.75-6). In the third cycle, Group A had a mean±SD of 4.50±1.31 follicles and Group B had 5.07±1.03, with median (IQR) values of 5 (3.25-5.75) and 5 (4-6), respectively. Across all cycles, the p-values for the comparison between the two groups were greater than 0.05, indicating no statistically significant differences in the number of growing follicles between the LNG-IUS and Dienogest groups (Table 4).

Table 4: Total number of Growing follicles following ovarian stimulation in Group A (Pre-treatment with LNG-IUS) and Group B (Pre-treatment with Dienogest) on D8 of folliculometry.

Number of growing follicles	Group A	Group B	P value
1st cycle	**(n=16)**	**(n=16)**	
Mean±SD	4.68±1.19	5.06±1.38	$^{m}0.38^{ns}$
Median (IQR)	5(4-5)	5 (4.25-6)	
2nd cycle	**(n=14)**	**(n=14)**	
Mean±SD	4.78±1.25	5.42±1.28	$^{m}0.26^{ns}$
Median (IQR)	4.5 (4-6)	5 (4.75-6)	
3rd cycle	**(n=12)**	**(n=13)**	
Mean±SD	4.50±1.31	5.07±1.03	$^{m}0.37^{ns}$
Median (IQR)	5 (3.25-5.75)	5 (4-6)	

Data presented as mean and SD. P-value reached through, m=Mann Whitney U-test for non-normally distributed continuous variables, ns=non-significant.

Table 5: Size of the Dominant follicles following ovarian stimulation in Group A (Pre-treatment with LNG-IUS) and Group B (Pre-treatment with Dienogest) on D12 of folliculometry.

Size of dominant follicle	Group A	Group B	P value
1st cycle	**(n=16)**	**(n=16)**	
Mean±SD	19.00±1.03	18.87±1.85	$^{m}0.56^{ns}$
Median (IQR)	19 (18-20)	18 (18-20)	
2nd cycle	**(n=14)**	**(n=14)**	
Mean±SD	19.50±1.16	19.64±1.98	$^{m}0.87^{ns}$
Median (IQR)	20 (18-20)	19.5 (18-20.50)	
3rd cycle	**(n=12)**	**(n=13)**	
Mean±SD	18.66±1.92	19.23±1.87	$^{m}0.50^{ns}$
Median (IQR)	19 (17-20)	18 (18-21)	

Data presented as mean and SD. P-value reached through, m=Mann Whitney U-test for non-normally distributed continuous variables, ns=non-significant.

The size of the dominant follicle was assessed in Group A and Group B across three cycles of treatment. In the first cycle, the mean±SD follicle size was 19.00±1.03 mm in Group A and 18.87±1.85 mm in Group B, with median (IQR) values of 19 (18-20) mm and 18 (18-20) mm, respectively (p=0.56, not significant). During the second cycle, Group A had a mean±SD size of 19.50±1.16 mm, while Group B recorded 19.64±1.98 mm; the median (IQR) values were 20 (18-20) mm for Group A and 19.5 (18-20.50) mm for Group B (p=0.87, not significant). In the third cycle, the mean±SD size was 18.66±1.92 mm in Group A and 19.23±1.87 mm in Group B, with median (IQR) values of 19 (17-20) mm and 18 (18-21) mm, respectively (p=0.50, not significant). Across all cycles, the differences in dominant follicle size between the two groups were minimal and not statistically significant (Table 5).

The endometrial thickness was evaluated in Group A and Group B over three treatment cycles. In the first cycle, the mean±SD thickness was 7.54±1.42 mm in Group A and 8.13±2.18 mm in Group B, with median (IQR) values of 7.5 (6.70-7.70) mm and 7 (6.25-10.40) mm, respectively (p=0.80, not significant). In the second cycle, Group A recorded a mean±SD thickness of 7.88±0.89 mm compared to 8.52±1.35 mm in Group B, with median (IQR) values of 7.8 (7-8.25) mm and 8 (7.72-9.37) mm, respectively (p=0.16, not significant). By the third cycle, Group A showed a mean±SD thickness of 7.86±1.26 mm, while Group B had 7.93±0.89 mm; the median (IQR) values were 7.7 (7-9.12) mm for Group A and 8 (7-8.25) mm for Group B (p=0.72, not significant) (Table 6).

The presence of ovulation signs was assessed in Group A and Group B over three treatment cycles. In the first cycle, ovulation signs were observed in 12 participants (75.0%) in Group A and 10 participants (62.5%) in Group B, while

no ovulation signs were recorded in 4 participants (25.0%) in Group A and 6 participants (37.5%) in Group B, with a relative risk (RR) of 1.2 (95% CI: 0.747–1.926) and a p-value of 0.45 (not significant). In the second cycle, signs of ovulation were observed in 12 participants (85.7%) in Group A and 8 participants (57.1%) in Group B, while 2 participants (14.3%) in Group A and 6 participants (42.9%) in Group B showed no signs, resulting in an RR of 1.50 (95% CI: 0.908–2.476) and a p-value of 0.11 (not significant). By the third cycle, ovulation signs were present in 8 participants (66.7%) in Group A and 8 participants (61.5%) in Group B, with 4 participants (33.3%) in Group A and 5 participants (38.5%) in Group B showing no signs, yielding an RR of 1.08 (95% CI: 0.602–1.948) and a p-value of 0.78 (not significant). Across all cycles, Group A consistently had a slightly higher percentage of ovulation signs compared to Group B, but the differences were not statistically significant (Table 7). The pregnancy rates were compared between Group A and Group B across three treatment cycles. In the first cycle, Group A had 1 pregnancy (6.3%) and Group B had 2 pregnancies (12.5%), with a relative risk (RR) of 0.50 (95% CI: 0.050 to 4.978) and a p value of 0.55, indicating no significant difference between the groups. In the second cycle, Group A had 2 pregnancies (14.3%) while Group B had none (0.0%), yielding an RR of 5.00 (95% CI: 0.261 to 95.612) and a p-value of 0.28, which was also not statistically significant. In the third cycle, neither group had any pregnancies (0.0%), resulting in an RR of 1.07 (95% CI: 0.023 to 50.437) and a p-value of 0.96, further showing no significant difference between the groups (Table 8).

The table compares adverse effects between Group A and Group B, each with 16 participants. A majority in Group A (68.8%) and over half in Group B (56.3%) reported no adverse effects, with no significant difference between the groups (p=0.97). Specific adverse effects such as gastrointestinal upset and headache occurred in 6.3% of participants in both groups. Breast tenderness and vaginal bleeding were slightly more common in Group B (12.5% each) compared to Group A (6.3% each). Weight gain was reported by 6.3% of participants in both groups. Overall, the incidence of adverse effects was similar, with no statistically significant differences observed (Table 9).

Table 6: The mean of endometrial thickness (mm) at Inj. HCG administration in group A (pre-treatment with LNG-IUS) and Group B (pre-treatment with dienogest) following ovarian stimulation.

Endometrium thickness	Group A	Group B	P value
1st cycle	**(n=16)**	**(n=16)**	
Mean±SD	7.54±1.42	8.13±2.18	$^{m}0.80^{ns}$
Median (IQR)	7.5 (6.70-7.70)	7 (6.25-10.40)	
2nd cycle	**(n=14)**	**(n=14)**	
Mean±SD	7.88±0.89	8.52±1.35	$^{m}0.16^{ns}$
Median (IQR)	7.8 (7-8.25)	8 (7.72-9.37)	
3rd cycle	**(n=12)**	**(n=13)**	
Mean±SD	7.86±1.26	7.93±0.89	$^{m}0.72^{ns}$
Median (IQR)	7.7 (7-9.12)	8 (7-8.25)	

Data presented as mean and SD. P-value reached through, m=Mann Whitney U-test for non-normally distributed continuous variables, ns=non-significant.

Table 7: Comparison of ovulation rate between group A (pre-treatment with LNG-IUS) and group B (pre-treatment with dienogest) following OS.

Sign of ovulation	Group A		Group B		RR	95% CI		P value
	(N)	(%)	(N)	(%)		Lower	Upper	
1st cycle	**(n=16)**		**(n=16)**					
Yes	12	75.0	10	62.5	1.2	0.747	1.926	$^{a}0.45^{ns}$
No	4	25.0	6	37.5				
2nd cycle	**(n=14)**		**(n=14)**					
Yes	12	85.7	8	57.1	1.50	0.908	2.476	$^{a}0.11^{ns}$
No	2	14.3	6	42.9				
3rd cycle	**(n=12)**		**(n=13)**					
Yes	8	66.7	8	61.5	1.08	0.602	1.948	$^{a}0.78^{ns}$
No	4	33.3	5	38.5				

Data presented as frequency and percentage over the columns. P-value reached through, a=Chi-square test for categorical variables, ns=non-significant, f=Fisher exact test for categorical variables, where expected value was <5 in ≥20% cells.

Table 8: Comparison of pregnancy rate between Group A (Pre-treatment with LNG-IUS) and Group B (Pre-treatment with Dienogest) following OS.

Pregnancy rate	Group A		Group B		RR	95% CI		P value
	(N)	(%)	(N)	(%)		Lower	Upper	
1st cycle	**(n=16)**		**(n=16)**					
Yes	1	6.3	2	12.5	0.50	0.050	4.978	f0.55
No	15	93.8	14	87.5				
2nd cycle	**(n=14)**		**(n=14)**					
Yes	2	14.3	0	0.0	5.00	0.261	95.612	f0.28
No	12	85.7	14	100.0				
3rd cycle	**(n=12)**		**(n=13)**					
Yes	0	0.0	0	0.0	1.07	0.023	50.437	f0.96
No	12	100.0	13	100.0				

Continued.

Data presented as frequency and percentage over the columns. P-value reached through, a=Chi-square test for categorical variables, ns=non-significant, f=Fisher exact test for categorical variables, where expected value was <5 in ≥ 20% cells.

Table 9: Adverse effects of group A (pre-treatment with LNG-IUS) and Group B (pre-treatment with dienogest) following OS.

Adverse effect	Group A (n=16)		Group B (n=16)		P value
	(N)	(%)	(N)	(%)	
No adverse effect	11	68.8	9	56.3	a0.97ns
GIT upset	1	6.3	1	6.3	
Headache	1	6.3	1	6.3	
Breast tenderness	1	6.3	2	12.5	
Vaginal bleeding	1	6.3	2	12.5	
Weight gain	1	6.3	1	6.3	

a=Chi-square test for categorical variables, ns=non-significant.

DISCUSSION

Adenomyosis is a benign uterine disorder marked by the presence of basal endometrial glands and stroma within the myometrium, often accompanied by hyperplasia of surrounding smooth muscle cells.[14] While previously diagnosed histopathologically, advances in imaging modalities such as MRI and high-resolution TVUS now allow for non-invasive diagnosis with 80%–90% accuracy.[15] Clinically, adenomyosis presents with an enlarged uterus, pelvic pain, heavy vaginal bleeding and impaired quality of life. Obstetric complications such as preterm delivery and premature rupture of membranes have also been associated with adenomyosis.[14] Its impact on fertility, however, remains inconclusive. Several mechanisms have been proposed, including disrupted sperm transport, elevated nitric oxide levels, altered uterine contractility and impaired implantation.[16,17]

The levonorgestrel-releasing intrauterine system (LNG-IUS), initially developed for contraception, has demonstrated non-contraceptive therapeutic benefits in conditions like menorrhagia and adenomyosis.[18,19] Dienogest (DNG), a synthetic oral progestin, is also effective for adenomyosis-related pain but is associated with discontinuation due to metrorrhagia.[20,21] Pre-treatment with either agent aims to alleviate symptoms and enhance fertility outcomes by improving the uterine environment.

This quasi-experimental study was carried out with an aim to evaluate and compare the fertility outcome following ovarian stimulation in infertile women pre-treated with LNG-IUS and dienogest for symptomatic adenomyosis. The results revealed slightly higher ovulation and pregnancy rates in the LNG-IUS group, though differences were not statistically significant (p>0.05). Ovulation-related factors were influenced by socio-demographic, clinical and sonographic characteristics. These findings support LNG-IUS as a viable, tolerable option with marginally better clinical outcomes.

There is lack of studies directly comparing the effectiveness of two pre-treatment LNG-IUS and Dienogest regarding fertility outcome. However, previous studies have independently assessed these agents. There have been studies on patients undergoing IVF after pre-treatment with LNG-IUS or Dienogest.[2,22] They are not comparable to our study as they used IVF protocol. Liang et al., showed clinical pregnancy rate was 44% (59/134) in pretreated LNG-IUS group and 33.5% in control group.[2] Aksenenko et al, showed pregnancy rate 35.3% in preparatory treatment with Dienogest group compared to 31.3% in control group.[22]

The mean age of participants in Group A was 30.81±3.14 years, while in Group B it was 31.18±3.03 years, showing no significant difference (p>0.05), which aligns with findings from Choudhury et al and Banu et al.[8,23] Educational attainment and occupational status were similar across groups, with most participants being housewives (78.5% in Group A and 75.0% in Group B). Similar demographics were reported by Banu et al, where 75% were housewives.[8]

Menstrual patterns were largely regular in both groups. Although group A reported higher cases of heavy bleeding (25.0% vs. 6.3%) and Group B showed more average blood loss (93.8%), the difference was not statistically significant (p=0.09). Banu et al, observed significant improvements in bleeding patterns, with complete resolution of heavy menstruation in the LNG-IUS group and persistence in 30% of the DNG group (p=0.012).[8] They also reported greater reductions in dysmenorrhea with LNG-IUS (p=0.001). VAS pain scores were higher in Group A (5.00±3.16) than in Group B (3.68±1.66), though not statistically significant (p=0.42). This corresponds with Choudhury et al, who found VAS scores of 6.41±1.07 (LNG-IUS) and 6.41±0.95 (DNG) and Banu et al, who reported higher baseline VAS scores in both groups.[8,23]

Hemoglobin levels did not differ significantly (10.80±1.04 in Group A vs. 11.00±0.97 in Group B, p=0.59), in line with other studies.[8,23] Uterine volume was larger in Group A (127.33±68.74 ml) compared to Group B (97.96±37.60 mL), with a trend toward significance (p=0.07). Banu et al, reported a significant decrease in uterine volume in LNG-IUS group at three months.[8]

Endometrial thickness was comparable: 4.70±0.50 mm in Group A and 4.85±0.79 mm in Group B (p=0.80), which aligns with Hou et al, who observed similar values of ~10.5 mm in both groups.[24] Antral Follicle Count (AFC) was also similar (8.81±1.16 in Group A vs. 9.68±2.21 in Group B, p=0.34), consistent with Liang et al.[2] Ovulation was observed slightly more in Group A across all cycles, though not significantly: first cycle (75% vs. 62.5%, p=0.45), second (85.7% vs. 57.1%, p=0.11) and third (66.7% vs. 61.5%, p=0.78).

Pregnancy rates were low and statistically comparable: first cycle (6.3% vs. 12.5%, p=0.55), second (14.3% vs. 0%, p=0.28) and third (0% in both). In comparison, Hou et al, reported higher clinical pregnancy rates per transfer: 63.8% in LNG-IUS vs. 50.5% in DNG.[24] Liang et al, also noted higher rates with LNG-IUS+stimulation (44.0% vs. 33.5%).[2]

Our study showed higher cumulative ovulation rate and pregnancy rate with LNG-IUS pre-treatment (76.1% and 7.1% respectively) compared to Dienogest pre-treatment (60.4% and 4.6% respectively) when both groups exposed to similar stimulation protocol. This is probably be explained by the systemic suppression of hypothalamus-pituitary-ovarian axis by dienogest in contrast to local effect of LNG-IUS. The LNG-IUS group demonstrated better ovarian response, a higher ovulation rate and an improved pregnancy rate in each cycle compared to the other group. In low resource settings LNG-IUS+Ovarian Stimulation might be considered as an alternate treatment option without ART assuming to give the best chance of becoming pregnant.

Adverse effects were similarly distributed 68.8% in Group A and 56.3% in Group B reported none (p=0.97). Common issues included gastrointestinal upset, headache, breast tenderness, vaginal bleeding and weight gain. Choudhury et al, found more adverse effects in the DNG group, particularly vaginal spotting (38.2% vs. 23.5%) and hot flushes (26.4% vs. 0%).[23]

The study's sample size was relatively small, which may limit the generalizability of the findings and the ability to detect smaller differences between the groups. The study was conducted over three cycles, due to restricted time frame, which may not be sufficient to observe long-term effects or outcomes of the treatments. The study was conducted at a single center, which may limit the external validity of the findings.

CONCLUSION

This study of infertile women of symptomatic adenomyosis pre-treated with LNG-IUS and Dienogest showed statistically no significant difference regarding ovarian response and achieving pregnancy rate following ovarian stimulation.

Recommendations

Future studies should include a larger sample size to enhance the statistical power and generalizability of the findings. Conducting studies over a longer duration to observe long-term effects and outcomes which will be helpful in low resource settings. Implementing multicenter trials to increase the external validity and applicability of the results across different populations and clinical settings.

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REFERENCES

1. Chen Q, Li YW, Wang S, Fan QB, Shi HH, Leng JH, et al. Clinical manifestations of adenomyosis patients with or without pain symptoms. J Pain Res. 2019;14:3127-33.
2. Liang Z, Yin M, Ma M, Wang Y, Kuang Y. Effect of pretreatment with a levonorgestrel-releasing intrauterine system on IVF and vitrified–warmed embryo transfer outcomes in women with

adenomyosis. Reproductive Bio Med. 2019;39(1):111-8.
3. Santulli P, Vannuccini S, Bourdon M, Chapron C, Petraglia F. Adenomyosis: the missed disease. Reproductive Bio Med. 2025;50(4):104837.
4. Dai Y, Leng J. The Surgical Treatment of Adenomyosis. Adenomyosis: Facts and treatments. 2021:99-111.
5. Puente JM, Fabris A, Patel J, Patel A, Cerrillo M, Requena A, et al. Adenomyosis in infertile women: prevalence and the role of 3D ultrasound as a marker of severity of the disease. Reproduct Bio Endocrinol. 2016;14:1-9.
6. Bourdon M, Oliveira J, Marcellin L, Santulli P, Bordonne C, Maitrot Mantelet L, et al. Adenomyosis of the inner and outer myometrium are associated with different clinical profiles. Human Reprod. 2021;36(2):349-57.
7. Wang WJ, Hao CF, Yin GJ, Bao SH, Qiu LH, Lin QD. Increased prevalence of T helper 17 (Th17) cells in peripheral blood and decidua in unexplained recurrent spontaneous abortion patients. J Reprod Immunol. 2010;84(2):164-70.
8. Banu J, Sultana S, Alamgir CF. Clinical efficacy of levonorgestrel releasing intrauterine system versus dienogest for women having symptomatic adenomyosis. Scholars International J Obst Gynecol. 2023;6(1):34–40.
9. Feng M, Chen LH, Hsu LT, Wu HM. Segmented in vitro fertilization and frozen embryo transfer in dienogest-treated patient with adenomyosis: A case report and lierature review. Taiwanese J Obstet Gynecol. 2022;61(5):906-8.
10. Liang T, Zhang W, Pan N, Han B, Li R, Ma C. Reproductive outcomes of in vitro fertilization and fresh embryo transfer in infertile women with adenomyosis: a retrospective cohort study. Front Endocrinol. 2022;13:865358.
11. Schindler AE. Dienogest in long-term treatment of endometriosis. International J Women's Health. 2011;6:175-84.
12. Yang Y, Li J, Chen H, Feng W. Assessment of risk factors associated with severe endometriosis and establishment of preoperative prediction model. Diagnostics. 2022;28;12(10):2348.
13. Akhigbe RE, Afolabi OA, Adegbola CA, Akhigbe TM, Oyedokun PA. Comparison of effectiveness of the levonorgestrel intrauterine system and dienogest in the management of adenomyosis: A systematic review and meta-analysis. European J Obstet Gynecol Reprod Biol. 2024;2:439.
14. Younes G, Tulandi T. Effects of adenomyosis on in vitro fertilization treatment outcomes: a meta-analysis. Fert Ster. 2017;108(3):483-90.
15. Maheshwari A, Gurunath S, Fatima F, Bhattacharya S. Adenomyosis and subfertility: a systematic review of prevalence, diagnosis, treatment and fertility outcomes. Human Repr. 2012;18(4):374-92.
16. Xiao Y, Li T, Xia E, Yang X, Sun X, Zhou Y. Expression of integrin β3 and osteopontin in the eutopic endometrium of adenomyosis during the implantation window. European J Obst Gynecol Reprod Biol. 2013;170(2):419-22.
17. Fischer CP, Kayisili U, Taylor HS. HOXA10 expression is decreased in endometrium of women with adenomyosis. Fert Ster. 2011;95(3):1133-6.
18. Fraser IS. Non-contraceptive health benefits of intrauterine hormonal systems. Contraception. 2010;82(5):396-403.
19. Ekin M, Cengiz H, Ayağ ME, Kaya C, Yasar L, Savan K. Effects of the levonorgestrel-releasing intrauterine system on urinary symptoms in patients with adenomyosis. European J Obst Gynecol Reprod Biol. 2013;170(2):517-20.
20. Fawzy M, Mesbah Y. Comparison of dienogest versus triptorelin acetate in premenopausal women with adenomyosis: a prospective clinical trial. Arch Gynecol Obst. 2015;292:1267-71.
21. Nagata C, Yanagida S, Okamoto A, Morikawa A, Sugimoto K, Okamoto S, et al. Risk factors of treatment discontinuation due to uterine bleeding in adenomyosis patients treated with dienogest. J Obstet Gynaecol Res. 2012;38(4):639-44.
22. Aksenenko AA, Ibragimova MK, Gavisova AA, Mishieva NG. Effectiveness of ivf in treating infertility in patients with internal endometriosis (adenomyosis). Obst Gynecol. 2021;15(1):120-5.
23. Choudhury S, Jena SK, Mitra S, Padhy BM, Mohakud S. Comparison of efficacy between levonorgestrel intrauterine system and dienogest in adenomyosis: a randomized clinical trial. Therap Advan Reproduc Health. 2024;18:2348.
24. Hou X, Xing J, Shan H, Mei J, Sun Y, Yan G, et al. The effect of adenomyosis on IVF after long or ultra-long GnRH agonist treatment. Reproductive biomedicine online. 2020;41(5):845-53.

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