Evaluation of efficacy of levonorgestrel-releasing intrauterine system (LNG-IUS) in pain management of endometriotic patients

Authors

1) **Aparna Nair, Associate Professor, Dept of OBG, Vydehi Institute of Medical Sciences & Research Institute, India.**
2) **B Gowthami, Assistant professor, Dept of OBG, Vydehi Institute of Medical Sciences & Research Institute, India.**
3) **Sampath Kumar, Professor, Unit chief, Dept of OBG, Vydehi Institute of Medical Sciences& Research Institute, India.**
4) **Sridhar Venkatesh, Professor, Unit chief, Dept of OBG, Vydehi Institute of Medical Sciences& Research Institute, India.**

Corresponding Author: Dr. Aparna Nair, Associate Professor, Dept of OBG, Vydehi Institute of Medical Sciences & Research Institute, India; Email: aparnaarunraj@gmail.com

Manuscript submitted – 3rd January 2022
Peer review completed – 9th April 2022
Accepted for Epub – 16th April 2023

Abstract:

Objective: In women with endometriosis who undergo laparoscopic cystectomy and adhesiolysis to compare efficacy of post-operative insertion of LNG IUS in reduction of pelvic pain and menorrhagia. Also, to compare the effect of LNG IUS insertion in improving quality of life score in these patients. **Methods**: This was a prospective interventional study on 52 women with stage 3 or 4 endometriosis who underwent laparoscopic cystectomy and adhesiolysis were allocated alternatively to either LNG IUS (n=26) or expectant management (n=26). VAS (Visual analogue scale), PGWBI (Psychological general well being index), MBS (Mean bleeding score) were used for objective assessment of pelvic pain, quality of life and menstrual bleeding respectively at the time of enrollment to study along with baseline parameters. Patients were called for review at 1st, 3rd and 6th month and parameters were compared in both groups. Additionally, it was notes if any additional analgesic was needed for pain relief in either group or any new complication developed during study period. **Results**: VAS score decreased significantly more in the study group from 6.92±2.04 to 2.60±0.92 by 6th month post insertion whereas in control group baseline score of 6.42±1.88 decreased to 4.42±0.99 at 6th month (p=<0.001). PGWBI scores were slightly better in the control group (45.73±10.80) than study group at the time of enrollment and this trend continued 1 month post insertion (47.08±10.59), difference was not statistically significant (p baseline =0.390, p 1 month=0.563). In study group PGWBI score improved from 43.00±11.88 (baseline) to 45.35±10.65 at 1st month and by 6th month scores improved significantly to 56.62±8.17. At 6th month control group PGWBI score was at 51.38±9.42. This difference was statistically significant (p=0.037). MBS of study group decreased from 3.20±0.51 at baseline to 2.02±0.42 by 6th month post LNG IUS insertion; MBS of control group decreased from baseline of 3.07±0.59 to 2.76±0.56 at 6th month (p<0.001). **Conclusion**: Patients with endometriosis have poor quality of life due to constant pain and irregular heavy cycles. It is beneficial to insert LNG IUS as it improves the quality of life most importantly, even in patients undergoing surgical treatment for the same.

Keywords: Endometriosis, LNG IUS, pelvis pain, visual analogue scale score, quality of life, menorrhagia.

Endometriosis is the growth of endometrial glands outside uterus that affects roughly 10% (190 million) women in reproductive age group globally [1]. It is a chronic disorder presenting with dysmenorrhea, menorrhagia, deep dyspareunia, and infertility. 60% of women with chronic pelvic pain have endometriosis [2]. Many theories are

Nair A, Gowthami B, Kumar S, Vankatesh S. Evaluation of efficacy of levonorgestrel-releasing intrauterine system (LNG-IUS) in pain management of endometriotic patients. The New Indian Journal of OBGYN. 16th April 2023. Epub Ahead of Print.

postulated but definite cause is still not established. It has a broad spectrum of presentation and prone to recurrence which adversely affects quality of life and leads to significant economic burden to the patient [2-4].

In the treatment of endometriosis various modalities are being used like GnRH analogue, laparoscopic cyst excision, danazol etc. Though, LNG IUS was devised in late 1970's for effective long acting contraception, this is also being tried as a treatment for endometriosis. It is already being used in disorders like adenomyosis, endometrial hyperplasia etc. LNG IUS releases levonorgestrel into endometrial cavity @ 20 micrograms /day for 5years after a single application without any systemic impact. Whereas the oral or injectable progesterone therapy which is used traditionally are known to have systemic adverse effects. Vercellini et al, the pioneers in using LNG IUS for endometriosis related dysmenorrhea found that postoperative recurrence of dysmenorrhea was significantly less in the LNG-IUS group [5].

Reduction in pelvic pain of patients with endometriosis after LNG IUS insertion could be explained by depletion of estrogen and progesterone receptors on ectopic endometrium or due to reduction in ectopic endometrial production of oestrogen-induced growth factors. LNG-IUS results in a decrease in endometrial proliferation and an increase in apoptosis in endometrial glands and stroma. There is increased FAS antigen and a decrease in Bcl-2 protein expression leading to apoptosis of the endometrium is postulated as one of the mechanism of action of LNG IUS [6]. Angiogenesis is a significant aspect of endometriosis pathology where ectopic endometrium is implanted into various parts of peritoneal cavity, ovary, pleural cavity etc. Vascular endothelial growth factor (VEGF) is a potent angiogenic factor involved in physiological and pathological angiogenesis, and elevated levels of VEGF are found in peritoneal fluid of patients with endometriosis hence LNG-IUS effect might be a function of a reduction of local vascular angiogenesis, a reduction in pelvic-vessel congestion and an increase in apoptosis, a reduction in peritoneal fluid macrophage activity and a modification in the production of cytokines responsible for maintenance of lesions and pain [7].

Vercellini et al in 2003 compared LNG IUS insertion to expectant management and found dysmenorrhea recurred more in only- surgery group at 1 year follow up compared to LNG IUS group[8]. Carllos A Petta et al in a study comparing LNG IUS and GnRH analogue in treatment of chronic pelvic pain associated with endometriosis, found both equally effective with additional advantage of LNG IUS that it does not provoke hypoestrogenism and requires medical intervention only once in 5 years [9]. Matorras R et al studied effectiveness of LNG IUS in treating pelvic pain in endometriotic patients where previous medical and surgical treatments have failed, reported that 70% patients had improvement in pain symptoms. They concluded LNG IUS should be considered before radical surgery is considered [10]. De Graff et al studied 909 women with endometriosis and found that quality of life was decreased in all eight dimensions of the SF-36v2 compared with norm-based scores from a general US population [4].

Though many international studies are conducted to check the effectiveness of LNG IUS in reducing pain associated with endometriosis, our aim is to study its effectiveness in reducing pain from endometriosis and if it correlates positively with improvement in quality of life and reduction in monthly bleeding for patient .

Materials and methods

This was a prospective interventional study conducted in the department of OBG, Vydehi Institute of Medical Sciences & Research Centre, Bengaluru, Karnataka, India. The study period was from November 2020 to December 2021. Approval from IEC and informed consent were obtained. Patients meeting the inclusion criteria were enrolled in the study and randomly allocated to study and control group.

Patients not on hormonal medication for endometriosis for six months or GnRH analogue injections for one year prior to enrolment were included in the study. All of them were willing to follow up for six months and did not wish to conceive for at least one year or had completed their family. None of them had any contraindication to use LNG-IUS as told by WHO (2004). They all were enrolled after undergoing laparoscopic cystectomy and adhesiolysis for endometriosis, and only stage 3 and 4 were included (ASRM criteria). Patients desirous of immediate fertility treatment or with any uterine or adnexal anomaly or associated PID and those unwilling to tolerate menstrual changes from LNG IUS were excluded from the study. In pre-treatment visit relevant data was collected from the patient by using pre structured proforma.

Tools used: VAS (Visual analogue scale), PGWBI (Psychological general well being index), MBS (Mean bleeding score) were used for objective assessment of pelvic pain, quality of life and menstrual bleeding respectively. The VAS is a straight line with the endpoints defining 0 as 'no pain at all' and 'pain as bad as it could be' as 10 [11]. The patient was asked to mark his pain level on the line between the two endpoints [12].

No pain ——————————————————————— Pain as bad as it could be.

The PGWBI (Psychological general well being index) questionnaire, which includes 22 items, allows to measure stress level by self-perceived evaluation [13]. Questions cover 6 aspects: anxiety, depressed mood, positive well-being, self-control, general health and vitality. Questions allow multiple choice answers with scores ranging from 0 to 5 (best score value). The PGWBI global score represents the sum of all items and ranges from 0 to 110. Higher scores indicate greater psychological well-being.

Bleeding score: Bleeding was assessed as - 0 = no bleeding; 1 = spotting (light bleeding not requiring sanitary protection); 2 = light bleeding (light bleeding requiring sanitary protection); 3 = normal bleeding (bleeding similar to normal menstrual blood flow); and 4 = heavy bleeding (bleeding exceeding normal menstrual blood flow). No bleeding was defined as 30 consecutive days with bleeding score of 0 [14]. The MBS was calculated by dividing the sum of the daily scores by the number of days in each observation period.

Baseline VAS, PGWBI, MBS were noted at enrolment visit preoperatively itself following which theyunderwent laparoscopic cystectomy and adhesiolysis. Day3 post laparoscopy women were classified into LNG or non-LNG group alternatively and LNG insertion was done at hospital before discharge. No adverse effect occurred post LNG IUS insertion. All women in both groups were requested to maintain a diary noting their - 1) daily pain score on VAS score, 2) daily bleeding score, 3) any additional analgesics used and 4) any other complications developing during study period. Both groups were followed up at 1 month, 3 month and 6 months post enrollment into study. At each visit we evaluated PGWBI score for quality of life for every patient. MBS and VAS scores were noted and compared with pretreatment scores in patients case file. Also, it was noted at each visit if any additional analgesics were required and in case any other complications occurred during follow up period like irregular bleeding, abdominal cramps etc.

Statistical analysis: Sample size calculation was done by: $N=2PQ\ (Z_{1}\text{-}\alpha/2 + Z_{1}\text{-}\beta)^2/(p_1\text{-}p_2)^2$

P_1=proportion of participants in first group with severe dysmenorrhea (10%)

P_2 = proportion of participants in 2nd group (45%)

$P = P_1+P_2$; $Q= 1-P$

$Z_{1}\text{-}\alpha/2 =1.96$ at 95% confidence interval; $Z_{1}\text{-}\beta = 0.84$ at 80% power

$P=0.1+0.45/2=0.275$. ; $Q=1-P = 0.725$

$N = 2\times0.275\times 0.725(1.96+0.84)^2/(0.35) = 26$ per group

Qualitative variable were presented as frequency and percentages. Quantitative variables were presented as mean ± standard deviation or median and IQR. To check for association between severity and groups, chi square test and student paired t test was performed.

Results

Totally 52 patients were enrolled during the thirteen months of study period. 26 women were allocated to each group. Average age (study group = 31.08±6.95 years; control group = 28.88 ± 5.74 years; p= 0.221), Educational status (p=0.849), residential location (p=0.405) and income range (p=0.756) were similar in both groups (table1). Age of menarche was around 12 years and was similar in both groups (study group -12.38±0.80 years; control group 12.81±0.85 years; p= 0.071). Primary complaint in both groups was severe dysmenorrhea, followed by chronic pelvic pain and menorrhagia (table1). Average duration of complaints was 26 months (table 1).19 (73.1%) women in study group and 18(69.2%) women in control group had posterior forniceal nodularity, but only 15(57.7%) in study group and 6 (23.1%) in control group reported dysparnuia. Most patients in both groups had regular cycles (18 in study group and 23 in control group). 42.3% and 53.8% women were nulligravida in study and control group

Table 1: Baseline parameters

Parameters	With mirena (Study)	Without mirena (Control)	P value
Age (Average age in years)	31.08±6.95	28.88±5.74	0.221
Educational status			
Illitrerate	6(23.1%)	6(23.1%)	
Schooling	8(30.8%)	8(30.8%)	0.849
Graduate	9(34.6%)	11(42.3%)	
Post graduate	3(11.5%)	1(3.8%)	
Locality			
Rural	11(42.3%)	14(53.8%)	0.405
Urban	15(57.7%)	12(46.2%)	
Income range			
<1L	4(15.4%)	5(19.2%)	
1-5L	11(42.3%)	13(50%)	0.756
>5L	11(42.3%)	8(30.8%)	
Age of menarche in years	12.38±0.80	12.81±0.85	0.071
Primary complaint			
Menorraghia	6 (23.07%)	3 (11.53%)	
Dysmenorrhea	12(46.15%)	14 (53.84%)	
Chronic pelvic pain	8 (30.76%)	9 (34.61%)	
Duration of complaints (in months)	25.54±17.61	27.12±19.13	P=0.75
Inferitility			
Yes	14 (53.84%)	15(57.69%)	
No	12 (46.15%)	11(42.30%)	
Dyspareunia	15 (57.7%)	12(46.15%)	
Bleeeding pattern			
Polymenorrhia (1)	8(30.8%)	2(7.7%)	0.075
Normal cycles (2)	18(69.2%)	23(88.5%)	
Hypomenorrhea (3)	0(0%)	1(3.8%)	
Any prior treatment (> 1yr prior)			
Yes	6 (23.1%)	7 (26.9%)	
No	20(76.9%)	19(73.1%)	
Obstetric h/o			
Nulligravida	11(42.30%)	12(53.84%)	
Parous	15(57.69%)	14(46.15%)	
Mode of delivery			
Vaginal	5(33.33%)	6(42.85%)	
LSCS	10(66.66%)	8(57.14%)	
Past medical h/o			
Yes	10(38.5%)	7(26.9%)	
No	16(61.5%)	19(73.1%)	
BMI (Kg/m^2)			
<18.5	0(0%)	0(0%)	0.072
18.5-24.9	4(15.4%)	9(34.6%)	
25-29	14(53.8%)	15(57.7%)	
30-34.9	8(30.8%)	2(7.7%)	
Post forniceal nodularity	19(73.1%)	18(69.2%)	0.375
Deep tenderness forniceal	20(76.9%)	18(69.2%)	0.229
R/V septum nodularity	19(73.1%)	18(69.2%)	0.375
USG findings			
U/L	11 (42.3%)	16 (61.5%)	
B/L	15(57.7%)	10(38.5%)	
Laparoscopy			
Stage 3	14(53.8%)	13(50%)	
Stage 4	12(46.2%)	13(50%)	

respectively. More than 50% of women in both groups reported infertility (study 53.84%; control 57.69%). History of infertility included both primary and secondary infertility.

Some women had taken medical treatment for endometriosis prior to this study (study group - 23.1%; control group - 26.9%). Few women had other associated medical disorders along with endometriosis, most common was hypothyroidism (study - 38.5%; control - 26.9%). Most women in study group (53.8%) and control group (57.7%) had BMI in the range of 25-29 kg/m^2. Endometriotic cyst was present bilaterally in 15 women (57.7%) in study group and 10 women (38.5%) in control group, rest were unilateral endometriotic cysts. None of the patients had undergone any surgery for endometriosis prior to laparoscopy done at our hospital.

Baseline score of 3 main variables at the onset of study were recorded. VAS score for pelvic pain in study group was 6.92±2.04 and in control group was 6.42±1.8, and the difference was not significant (p=0.362). PGWBI score to assess quality of life was 43±11.88 in study group and 45.73±10.8 in control group, the difference was not statistically significant (p= 0.390). MBS per month in study and control group was 3.20±0.51 and 3.07± 0.59 respectively and there was no statistical significance in both the groups (p=0.408).

VAS score decreased in the study group from 6.92±2.04 to 2.60±0.92 by 6th month post insertion whereas in control group baseline score of 6.42±1.88 decreased to 4.42±0.99 at 6th month (p=<0.001) (table 2) (figure 1).

Table 2: VAS Score for pelvic pain baseline and post insertion in both study and control group

VAS	Control group	Study group	Total	P value
Base	6.42±1.88	6.92±2.04	6.67±1.96	0.362
1 month post insertion	5.67±1.57	6.06±1.77	5.87±1.67	0.411
3 months post insertion	4.81±1.27	4.35±1.24	4.58±1.26	0.190
6 months post insertion	4.42±0.99	2.60±0.92	3.51±1.32	<0.001**

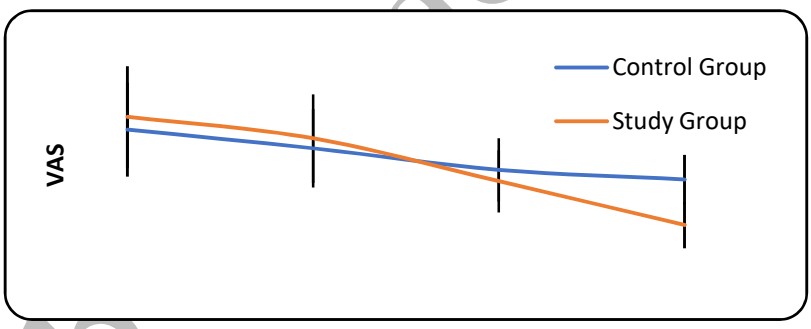

Figure 1: Line graph depicting improvement in VAS score for pain in study and control group

PGWBI scores were slightly better in the control group (45.73±10.80) than study group at the time of enrollment and this trend continued 1 month post insertion (47.08±10.59), though the difference was not statistically significant (p baseline = 0.390, p 1 month = 0.563). In study group PGWBI score improved from 43.00±11.88 (baseline) to 45.35±10.65 at 1st month and by 6th month scores improved significantly to 56.62±8.17. At 6th month control group PGWBI score was at 51.38±9.42. This difference was statistically significant (p=0.037) (table 3) (figure 2).

Table 3: PGWBI score for quality of life

Quality	Control group	Study group	Total	P value
Base	45.73±10.80	43.00±11.88	44.37±11.33	0.390
1 month post insertion	47.08±10.59	45.35±10.85	46.21±10.65	0.563
3 months post insertion	49.81±10.00	50.00±10.00	49.90±9.90	0.945
6 months post insertion	51.38±9.42	56.62±8.17	54.00±9.12	0.037*

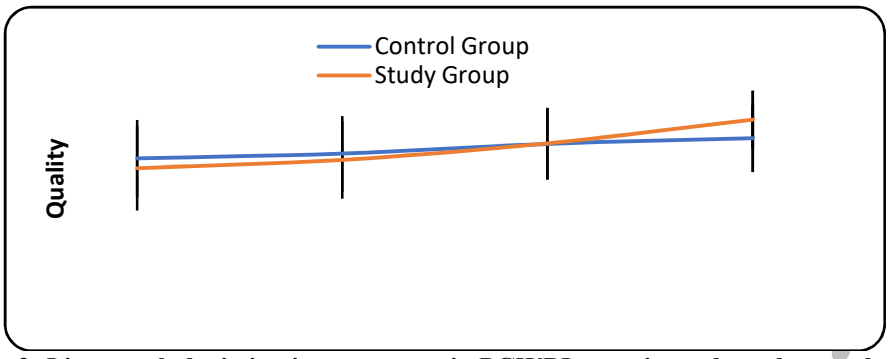

Figure 2: Line graph depicting improvement in PGWBI score in study and control group.

MBS of study group decreased from 3.20±0.51 at baseline to 2.02±0.42 by 6th month post LNG IUS insertion; MBS of control group decreased from baseline of 3.07±0.59 to 2.76±0.56 at 6th month. By 6th month MBS was significantly lesser in study group (p<0.001) (table 4) (figure 3).

Table 4 : MBS score for bleeding in study and control group

MBS	Control group	Study group	Total	P value
Base	3.07±0.59	3.20±0.51	3.14±0.55	0.408
1 month post insertion	2.87±0.58	3.00±0.50	2.93±0.54	0.388
3 months post insertion	2.77±0.57	2.57±0.49	2.67±0.54	0.173
6 months post insertion	2.76±0.56	2.02±0.42	2.39±0.62	<0.001**

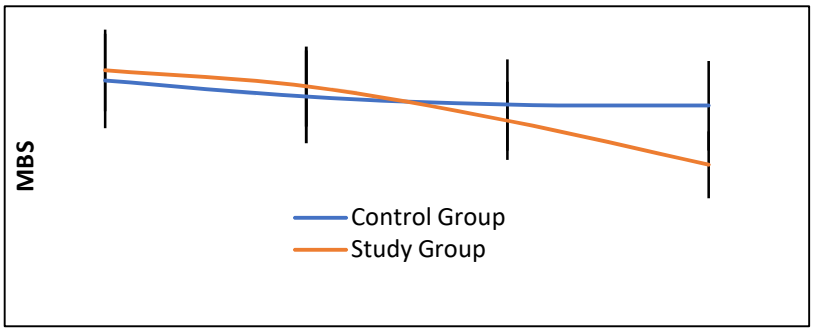

Figure 3: Line graph depicting improvement in bleeding score in study and control group.

Table 5: Need for additional analgesics and any complication during follow up period

Additional analgesic	Control group	Study group	Control group	Study group	Control group	Study group
	1 month follow up		3rd month follow up		6th month follow up	
Needed in patients	4	6	3	0	2	0
Any complication						
Breast tenderness	0	0	0	4	0	6
Non specific	0	0	0	1	0	0
Irregular bleed	3	0	3	1	2	0
Abdominal cramps	0	0	0	2	2	0
USG at 6 months (recurrence of endometrioma noted)					2	0

Complication noted in study and control group were breast tenderness, irregular bleeding, abdominal cramps and generalized complaints like bloating, dyspepsia etc. Among this breast tenderness was significantly more in study group compared to control group. Irregular bleeding was more in control group (table 5). 2 patients in control group

and none in study group required additional analgesics by 6th month. At 6th month follow up USG was done for all patients 2 patients in control group and none in study group had recurrence of ovarian cyst.

Discussion

Baseline parameters in both study and control group were comparable, like that by other authors Vercillini P et al, Petta CA et al, Taneja A et al, Tanmahasamut P et al who had similar findings [8,9,15,16]. Treolar et al stated age of menarche after 14 years was strongly and inversely associated with endometriosis, similar to this study wherein all the patients had average age of menarche as 12.60±0.85 years [17,18].

According to Treolar et al, Missimer et al and Matalliotakis et al endometriosis was more in women with lower BMI, but in this study the average BMI of women was in the range of 25-29 kg/m^2 [17-19]. Primary complaint in most of our patients was dysmenorrhea and around 50% of women in both groups complained of dysparunia, like that conducted by Sinaii et al, who studied 1000 women with endometriosis among which 79% of them complained of dysmenorrhea and 39.5% had dyspareunia [20]. J Perscott et al noted that women with endometriosis had 2-fold increased risk of infertility and endometriosis was a significant risk factor for infertility in women less than 35 years of age [21]. In our study more than 50% of women in both groups had either primary or secondary infertility. This is similar to the historical article by Counsellor VS who noted that about 25 to 50% of infertile women have endometriosis, and 30 to 50% of women with endometriosis are infertile [22]. Study conducted by Jin-Sung Yuk et al found Graves' disease associated with endometriosis but not hypothyroidism but in this study hypothyroidism was the most common medical disorder among all the patients with endometriosis [23].

As all the patients included in the study underwent laparoscopic cystectomy, there was significant reduction in pain scores in both groups at 1st month post operatively. This difference in VAS score between control group and study group at 1st month was not significant (p=0.41), like observation by Petta CA et al and Tekin Y et al [9,24]. In fact, at 1st month follow up visit control group had lower VAS score and lesser bleeding score than study group with LNG IUS insertion.

In this study, VAS score decreased in study group by 3rd month from 6.92±2.04 to 4.4 ±1.2 and in control group from 6.42±1.88 to 4.8±1.3 (p=0.41), similar to study by Taneja et al [15]. VAS score for study group with LNG IUS had significantly lower (2.6±0.92) than control group (4.42±0.99) at 6th month and the difference was statistically significant (p<0.001). Tanmahasamut et al found similar result when they conducted a double blind randomized controlled trial on 55 patients with endometriosis and found greater reduction in dysmenorrhea in group with LNG IUS [16]. This observation is different from that of Carlos A Petta who compared between LNG IUS and GnRH and both groups had similar pain scores by end of 6th month [9]. At the end of 6th month all the parameters evaluated were better in study group compared to control group, need for additional analgesic was lesser, and recurrence of ovarian cyst was lesser in study group, like the results of a meta-analysis by Song SY et al which concluded that LNG was as effective as GnRH in reducing pain and reduced recurrence rate of endometriosis [25].

Endometriosis affects a woman psychologically due to constant pelvic pain, dyspareunia, dyschazia etc. Assessment of this aspect of the disease was to understand if insertion of LNG IUS will significantly improve quality of life of patients post insertion due to pain relief. As noted by Lowe et al endometriotic patients had higher psychoticism, introversion, and anxiety scores [26]. Similarly, Sepulcri et al studied 104 endometriotic women and found depression, anxiety higher in them with substandard quality of life. They concluded that treatment of endometriosis should include evaluation of emotional profile and quality of life [27, 28]. Average PGWBI score in this study was 44.37±11.33 denoting low quality of life. The PGWBI score improved from 43±11.88 to 56.6±8.2 by 6th month in study group and from 45.7±10.8 to 51.38 ±9.42 in control group. The difference in improvement of quality of life at 3rd month was not significant between both groups (p=0.95), but by 6th month quality of life significantly improved for the study group with LNG IUS (p=0.037). This finding was different from that of Tekin et al in Turkey who found lower patient satisfaction among LNG IUS users compared to women who received GnRH [24]. Ozdegirmenci O et al had noted insertion of LNG IUS improved quality of life in women with adenomyosis [29].

Mean bleeding scores (MBS) decreased by sixth month in both groups but was more in LNG IUS group (2.02 ± 0.42) compared to control group (2.76 ± 0.56), and the difference was statistically significant ($p<0.001$) which is similar to findings by Wong et al [30].

There is scarcity of literature review regarding benefit of LNG IUS in improving quality of life in endometriotic patients. This study was an effort to prove that LNG IUS is a viable long-term option for women suffering endometriosis. It requires only single time medical intervention in 5 years, has minimal systemic side effects compared to Inj. GnRH, injectable DMPA, danazol etc. and is less radical than hysterectomy and bilateral salphingo-oophorectomy [9,15].

Complications in this study were breast tenderness, irregular bleeding, abdominal cramps, bloating etc. Breast tenderness was noted to be more in study group and irregular bleeding was more in control group this was similar to findings by other authors [30 - 32]. Recurrence of ovarian endometrioma was seen in 2 cases of control group and none in study group. Koga et al noted 30.4% as recurrence rate at 2 years follow up [33].

Conclusion

Patients with endometriosis have poor quality of life due to constant pain and irregular heavy cycles. It is beneficial to insert LNG IUS as it improves the quality of life most importantly, even in patients undergoing surgical treatment for the same.

References

1. WHO. Endometriosis. Geneva: WHO; 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/endometriosis.

2. Fritz MA, Speroff L. Clinical gynecologic endocrinology and infertility. 8th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011. pp. 32122.

3. Simoens S, Dunselman G, Dirksen C, Hummelshoj L, Bokor A, Brandes I, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. Hum Reprod. 2012 May; 27(5):1292-9.

4. De Graaff AA, D'Hooghe TM, Dunselman GA, Dirksen CD, Hummelshoj L, WERF Endo Cost Consortium, et al. The significant effect of endometriosis on physical, mental and social wellbeing: results from an international cross-sectional survey. Hum Reprod. 2013 Oct; 28(10): 2677-85.

5. Vercellini P, Aimi G, Panazza S, De Giorgi O, Pesole A, Crosignani PG. A levonorgestrel-releasing intrauterine system for the treatment of dysmenorrhea associated with endometriosis: a pilot study. Fertil Steril. 1999 Sep; 72(3): 505-8.

6. Maruo T, Laoag-Fernandez JB, Pakarinen P, Murakoshi H, Spitz IM, Johansson E. Effects of the levonorgestrel-releasing intrauterine system on proliferation and apoptosis in the endometrium. Hum Reprod. 2001 Oct; 16(10): 2103-8.

7. McLaren J, Prentice A, Charnock-Jones DS, Millican SA, Müller KH, Sharkey AM, et al. Vascular endothelial growth factor is produced by peritoneal fluid macrophages in endometriosis and is regulated by ovarian steroids. J Clin Invest. 1996 Jul 15; 98(2): 482-9.

8. Vercellini P, Frontino G, De Giorgi O, Aimi G, Zaina B, Crosignani PG. Comparison of a levonorgestrel-releasing intrauterine device versus expectant management after conservative surgery for symptomatic endometriosis: a pilot study. Fertil Steril. 2003; 80: 305-9.

9. Petta CA, Ferriani RA, Abrao MS, Hassan D, Rosa E Silva JC, Podgaec S, et al. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. Hum Reprod. 2005 Jul; 20(7):1993-8.

10. Matorras R, Ballesteros A, Prieto B, Ocerin I, Expósito A, Pijoan JI, et al. Efficacy of the levonorgestrel-releasing intrauterine device in the treatment of recurrent pelvic pain in multi-threaded endometriosis. J Reprod Med. 2011 Nov-Dec; 56(11-12): 497-503.

11. Glossary. Spine. 200; 25: 3200-2. Available from: https://journals.lww.com/spinejournal/Citation/2000/12150/Glossary.16.aspx

12. Freyd M. The graphic rating scale. J Educ Psychol. 1923; 43: 83-102

13. Grossi E, Mosconi P, Groth N, Niero M, Apolone G. Development and validation of the short version of thePsychological General Well-Being Index (PGWB-S). Milano: BioMed Central Ltd; 2002.

14. Rodriguez G, Faundes A, Atkinson LE. An approach to the analysis of menstrual patterns in the clinical evaluation of contraceptives. Stud Fam Plann. 1976; 7: 42-51.

15. Taneja A, Kaur S, Soni RK, Bhanupriya, Kaur J, Singla L. Evaluating the Efficacy of Levonorgestrel Intrauterine System and Danazol for Relief of Postoperative Pain in Endometriosis. J Clin Diagn Res. 2017; 11(7): QC10-QC12.

16. Tanmahasamut P, Rattanachaiyanont M, Angsuwathana S, Techatraisak K, Indhavivadhana S, Leerasiri P. Postoperative levonorgestrel-releasing intrauterine system for pelvic endometriosis-related pain: a randomized controlled trial. Obstet Gynecol. 2012 Mar; 119(3): 519-26.

17. Treloar SA, Bell TA, Nagle CM, Purdie DM, Green AC. Early menstrual characteristics associated with subsequent diagnosis of endometriosis. Am J Obstet Gynecol. 2010 Jun; 202(6): 534. e1-6.

18. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. Incidence of Laparoscopically Confirmed Endometriosis by Demographic, Anthropometric, and Lifestyle Factors. American Journal of Epidemiology. 2004;160(8): 784-96.

19. Matalliotakis I, Cakmak H, Fragouli Y, Goumenou A, Mahutte N, Arici A. Epidemiological characteristics in women with and without endometriosis in the Yale series. Archives of Gynaecology and Obstetrics. 2008; 277(5): 389-93.

20. Sinaii N, Plumb K, Cotton L, Lambert A, Kennedy S, Zondervan K, et al. Differences in characteristics among 1,000 women with endometriosis based on extent of disease. Fertil Steril. 2008 Mar; 89(3): 538-45.

21. Prescott J, Farland LV, Tobias DK, Gaskins AJ, Spiegelman D, Chavarro JE, et al. A prospective cohort study of endometriosis and subsequent risk of infertility. Hum Reprod. 2016 Jul; 31(7): 1475-82.

22. Counsellor VS. Endometriosis. A clinical and surgical review. Am J Obstet Gynecol. 1938; 36: 877.

23. Jin-Sung Y, Eun-Ju P, Yong-Soo S; Hee Jin K; Seon-Young K; Won IP. Graves Disease Is Associated With Endometriosis. Medicine. March 2016; 95(10): e2975

24. Bayoglu Tekin Y, Dilbaz B, Altinbas SK, Dilbaz S. Postoperative medical treatment of chronic pelvic pain related to severe endometriosis: levonorgestrel-releasing intrauterine system versus gonadotropin-releasing hormone analogue. Fertil Steril. 2011 Feb; 95(2): 492-6.

25. Song SY, Park M, Lee GW, Lee KH, Chang HK, Kwak SM, et al. Efficacy of levonorgestrel releasing intrauterine system as a postoperative maintenance therapy of endometriosis: A meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2018 Dec; 231: 85-92.

26. Low WY, Edelmann RJ, Sutton C. A psychological profile of endometriosis patients in comparison to patients with pelvic pain of other origins. J Psychosom Res. 1993; 37(2):111-6.

27. Sepulcri Rde P, do Amaral VF. Depressive symptoms, anxiety, and quality of life in women with pelvic endometriosis. Eur J Obstet Gynecol Reprod Biol. 2009 Jan; 142(1): 53-6.

28. Tripoli TM, Sato H, Sartori MG, de Araujo FF, Girão MJ, Schor E. Evaluation of quality of life and sexual satisfaction in women suffering from chronic pelvic pain with or without endometriosis. J Sex Med. 2011 Feb; 8(2):497-503.

29. Ozdegirmenci O, Kayikcioglu F, Akgul MA, Kaplan M, Karcaaltincaba M, Haberal A, et al. Comparison of levonorgestrel intrauterine system versus hysterectomy on efficacy and quality of life in patients with adenomyosis. Fertil Steril. 2011 Feb; 95(2): 497-502.

30. Wong AYK, Tang LCH, Chin RKH. Levonorgestrel-releasing intrauterine system (Mirena) and Depot medroxyprogesterone acetate (Depoprovera) as long-term maintenance therapy for patients with moderate and severe endometriosis: A randomised controlled trial. The Australian & New Zealand journal of obstetrics & gynaecology. 2010; 50(3): 273-9.

31. Chen YJ, Hsu TF, Huang BS, Tsai HW, Chang YH, Wang PH. Postoperative maintenance levonorgestrel-releasing intrauterine system and endometrioma recurrence - A randomized controlled study. American Journal of Obstetrics and Gynecology. 2017; 216 (6): 582.e1-e9.

32. Kim MK, Chon SJ, Lee JH, Yun BH, Cho SH, Choi YS, et al. Postoperative Levonorgestrel-Releasing Intrauterine System Insertion After Gonadotropin – Releasing Hormone Agonist Treatment for Preventing Endometriotic Cyst Recurrence: A Prospective Observational Study. Reproductive sciences. 2018 Jan; 25(1): 39-43.

33. Koga K, Takemura Y, Osuga Y, Yoshino O, Hirota Y, Hirata T, et al. Recurrence of ovarian endometrioma after laparoscopic excision. Human Reproduction. 2006; 21(8): 2171-74.

Conflict of interest: None. **Disclaimer:** Nil.