Levonorgestrel-releasing intrauterine system is An Efficient Therapeutic Modality for Simple Endometrial Hyperplasia

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Abstract: Objectives: To evaluate the therapeutic outcome of local (L) versus oral (O) progestins for management of simple endometrial hyperplasia (SEH). **Patients & Methods:** The study included 84 multiparous women with mean age of 41.7±4.7 years; 68 were pre- and 16 were post-menopausal women presented by abnormal uterine bleeding (AUB). Patients were divided into two equal groups: Group O received norethisterone acetate (NET) (15 mg/day as continuous oral dose for 3 months) and Group L assigned to Levonorgestrel-releasing intrauterine system (LNG-IUS) insertion. Primary outcome was to define number of responders after 3 months (Phase I). Responders were continuously followed-up, while non-responders in each group received the program assigned for the other group for another 3-months (Phase II) and all non-responders after Phase II were assigned for hysterectomy. Secondary outcome was the duration and severity of menstrual bleeding and the occurrence of spotting during duration of cycle. Patients' satisfaction at the end of the study period was evaluated. **Results**: Primary outcome of Phase I was 73.8% in group L and 57.1% in group O with significantly higher frequency of responders in group L. During Phase II, 72.2% patients responded to LNG-IUS compared to 63.6% response to NET therapy and 9 patients (10.7%) had hysterectomy. Both therapeutic regimens significantly reduced duration and heaviness of blood loss with significant reduction at 6-m compared to 3-m and in group L compared to group O. Throughout follow-up period of 15.3±4.2 months, no case progressed to atypical EH or carcinoma. At the end of follow-up, the frequency of higher satisfaction grades was significantly higher in group L compared to group O. **Conclusion:** LNG-IUS is safe and efficient therapeutic modality for SEH in women with AUB. LNG-IUS significantly reduced hysterectomy rate and duration and severity of bleeding with high satisfaction rates. LNG-IUS could be used as prophylactic therapy as no patient progressed to atypia or cancer.

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1.Introduction:

Endometrial hyperplasia (EH) represents a spectrum ranging from an exaggerated physiologic state to carcinoma in situ. EH mostly occurs secondary to an unopposed estrogen stimulation in the absence of progestin influence. EH are important clinically because they may cause abnormal uterine bleeding, and precede or occur concurrently with endometrial carcinoma. Cytologic atypia is the most important risk factor for progression to carcinoma. However, EH without atypia (Simple EH) was characterized by its low malignant potential, high rate of spontaneous resolution and the therapeutic response to oral progesterone is also high. Therefore, hysterectomy for EH without atypia may be regarded as an over-treatment [1, 2, 3].

Progesterone is a key hormone in regulating the female reproductive system, interacting at the level of the hypothalamus, the ovary, the uterus and the breast. Progesterone exerts effects on ovulation, endometrial differentiation, cervical mucus, breast differentiation and uterine contractility. Progestins and their analogs and antagonists have many uses in gynecology including contraception, management of miscarriage, medical abortion and treatment of conditions related to endometrial and myometrial growth and development. Beyond providing highly effective contraception, intrauterine delivery is safe and effective in the management of menorrhagia, dysmenorrhea, uterine myomata, and endometrial proliferation [4, 5, 6].

Conservative treatment has been considered to be acceptable when the strict follow-up is possible to detect cases of persistence, recurrence, and progress to carcinoma. Oral progesterone has been used to treat women with EH who wish to conserve the uterus. But some systemic side effects and poor compliance have been reported to be associated with oral progesterone [7, 8].

Intrauterine delivery of progestin is an effective way to administer local treatment and bypass systemic side effects. Intrauterine drug delivery has the potential to treat many gynecologic conditions, but is under utilized because clinicians lack knowledge and skills and because the current delivery systems are unavailable or costly in many

countries. Compared with oral progesterone, LNG-IUS has been reported to have less systemic side effects and higher efficacy for the treatment of EH in many studies targeting the women of western countries [9, 10, 11].

The current prospective comparative study aimed to evaluate the therapeutic outcome of local versus oral progestins for management of simple endometrial hyperplasia.

2. Patients & Methods

The current study was conducted at Obstetrics and Gynecology Department, Benha University Hospital since June 2011 till April 2013 to allow 6 months follow-up period for the last case enrolled in the study. After approval of the study protocol by the Local Ethical Committee and obtaining patients' written fully informed consent, all women with abnormal uterine bleeding (AUB) attending the Gynecology outpatient clinic were enrolled in the study.

A detailed history, clinical examinations and ultrasound evaluation were carried out. Endometrial biopsy samples were obtained by hysteroscopy and sent for histopathological examination. EH was divided into 4 categories according to the Kurman criteria: simple hyperplasia without atypia, complex hyperplasia without atypia, simple hyperplasia with atypia, and complex hyperplasia with atypia [12]; only patients with simple EH without atypia were included in the study. Patients with other pathology e.g., submucosal myomas or polyps, adnexal abnormality, genital infection, hormone therapy or any medication which might affect the menstrual blood loss within the previous 6 months e.g., steroid hormones or anticoagulants, previous endometrial ablation, diabetic and/or hypertensive patients were excluded from the study.

All patients were assigned to undergo the study in a period between bleeding attacks . Patients were randomly, using sealed envelops, allocated into two groups: Group O: included patients assigned to receive norethisterone acetate (NET) continuously in a dose of 15 mg/day and Group L: included patients assigned to apply Levonorgestrel-releasing intrauterine system (LNG-IUS). Insertion of LNG-IUS was performed one day after cessation of bleeding. The uterine cavity length was measured using uterine sounding, followed by LNG-IUS insertion. Accurate LNG-IUS position was documented with transvaginal ultrasonography immediately after insertion.

The primary outcome of the Phase I of the study was to define number of responders after 3 months of treatment. Endometrial specimens were obtained at the end of the three months using pipelle catheter. The outcome was determined by comparing the diagnosis of the 3-m biopsy with the diagnosis of the initial baseline biopsy. Response to treatment based on the last curettage specimen was defined as: Responders if the 3-m biopsy diagnosis was secretory-, inactive- or atrophic-pattern endometrium (Resolution) or proliferative pattern endometrium (regression) and Non-responders if the 3-m biopsy diagnosis was SEH (Persistence) or was complex EH (Progression) [13]. The secondary outcome of the study was the duration and severity of uterine bleeding and the occurrence of spotting during duration of cycle. Heaviness of bleeding was graduated using the pictorial blood assessment chart [14] as shown in table (1). Bleeding was assessed at time of enrolment in the study (Baseline assessment) and at the end of 3 and 6 months.

Table (1): The pictorial blood assessment chart [14]

Towels	Lightly stained tampon Moderately stained tampon Tampon is completely saturated with blood	1 point 5 points 20 points
Tampons	Lightly stained tampon Moderately stained tampon Tampon is completely saturated with blood	1 point 5 points 20 points
Clots	Small clot Large clot	1 point 5 points

Responders were continuously followed-up clinically every 3 months, while non-responders in each group were assigned to receive the program assigned for the other group for another 3-months (Phase II) and the response rate after shifting was defined. All Phase II non-responders were assigned for hysterectomy. Patients' satisfaction at the end of the study period was graded as using Likert-type scale, with 5 indicating "excellent," 4 "very good," 3 "good," 2 "fair," and 1 "poor" [15].

Statistical analysis

Obtained data were presented as mean±SD, ranges, numbers and ratios. Results were analyzed using Wilcoxon; ranked test for unrelated data (Z-test) and Chi-square test (X^2 test). Statistical analysis was conducted using the SPSS (Version 15,

2006) for Windows statistical package. *P* value <0.05 was considered statistically significant.

3. Results

The study included 84 women with mean age of 41.7±4.7; range 33-51 years. Sixteen women were post-menopausal, while 68 women were premenopausal. All were multipara with a mean parity of 3.2±0.8; range: 2-5. Forty-six women (54.8%) had vaginal delivery, while 38 women (45.2%) had previous cesarean sections. Previous contraception was using pills (29 women; 34.5%) or cupper IUD (33 women; 39.3%); 15 women (15.5%) were acclimatized to use safe period and 9 women (10.7%) used condom, (Table 2).

Table (2): Patients' demographic data

Data			Group O (n=42)	Group L (n=42)	Total (n=84)
Age (years)	Mean±SD		40.5±4.6	41.8±4.9	41.7±4.7
	Strata	<35	0	1 (2.4%)	1 (1.2%)
		35-<40	22 (52.4%)	19 (45.2%)	41 (48.8%)
		40-<45	12 (28.6%)	10 (23.8%)	22 (26.2%)
		45-<50	8 (19%)	9 (21.4%)	17 (20.2%)
		>50	0	3 (7.2%)	3 (3.6%)
Menopause	Pre		35 (83.3%)	33 (78.6%)	68 (81%)
	Post		7 (16.7%)	9 (21.4%)	16 (19%)
Parity	Mean±SD		3.1±0.8	3.3±0.9	3.2±0.8
	Strata	2	9 (21.4%)	6 (14.3%)	15 (17.9%)
		3	22 (52.4%)	23 (54.8%)	45 (53.6%)
		4	8 (19%)	9 (21.4%)	17 (20.2%)
		5	3 (7.2%)	4 (9.5%)	7 (8.3%)
Mode of delivery	Vaginal		24 (57.1%)	22 (52.4%)	46 (54.8%)
	Cesarean section		18 (42.9%)	20 (47.6%)	38 (45.2%)
Contraceptive history	Pills		13 (31%)	16 (38.1%)	29 (34.5%)
	Cupper IUD		17 (40.5%)	16 (38.1%)	33 (39.3%)
	Safe period		7 (16.7%)	6 (14.3%)	13 (15.5%)
	Condom		5 (11.8%)	4 (9.5%)	9 (10.7%)

Data are presented as mean±SD & numbers; ranges & percentages are in parenthesis

Primary outcome of Phase I was 73.8% in group L and was 57.1% in group O with significantly (X^2=3.15, p<0.05) higher frequency of responders in group L compared to group O. Primary outcome of Phase II was 72.2% in patients received LNG-IUS compared to 63.6% in patients received NET therapy with non-significantly (X^2=1.743, p>0.05) higher frequency of responders with LNG-IUS compared NET therapy. Nine patients had hysterectomy for a rate of 10.7% with non-significantly (X^2=0.417, p>0.05) higher frequency with oral therapy compared to local therapy, (Fig. 1).

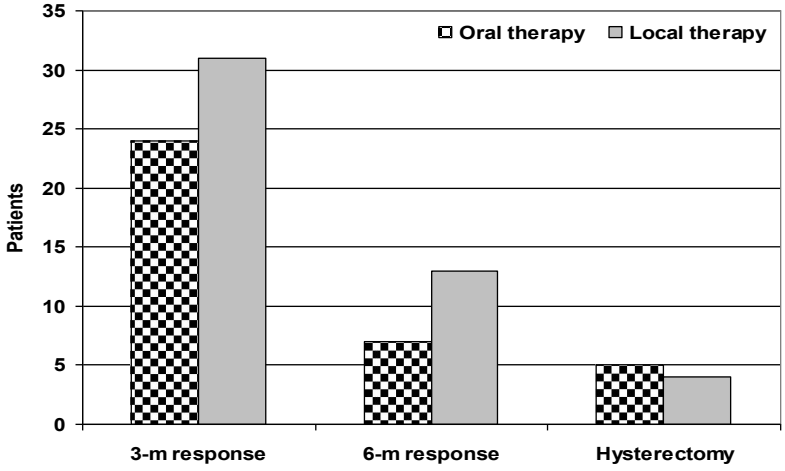

Fig. (1): Response rate to therapeutic regimen used

During Phase I, 21 patients had inactive endometrium, 13 patients had atrophic endometrium, 11 patients had secretory endometrium and 10 patients had proliferative endometrium with non-significantly (X^2=2.284, p>0.05) higher frequency of inactive and atrophic endometria in group L compared to group O. During Phase II, 9 patients had inactive endometrium, 7 patients had atrophic endometrium, 3 patients had secretory endometrium and one patient treated by NET had proliferative endometrium with non-significant (X^2=2.125, p>0.05) higher frequency of inactive and atrophic endometria in group L compared to group O, (Table 2).

Table (2): Patients' distribution according to histopathological diagnosis of endometrial biopsies taken at the end of 3- and 6- months

			Group O	Group L	Statistical significance
Phase I	Responders	Secretory	6 (14.3%)	5 (11.9%)	X^2=2.284, p>0.05
		Inactive	8 (19%)	13 (31%)	
		Atrophic	4 (9.5%)	9 (21.4%)	
		Proliferative	6 (14.3%)	4 (9.5%)	
		Total	24 (57.1%)	31 (73.8%)	
	Non-responders	Persistent	18 (42.9%)	11 (26.2%)	
Phase II	Responders	Secretory	1 (9.1%)	2 (11.1%)	X^2=2.125, p>0.05
		Inactive	3 (27.3%)	6 (33.3%)	
		Atrophic	2 (18.2%)	5 (27.8%)	
		Proliferative	1 (9.1%)	0	
		Total	7 (16.7%)	13 (31%)	
	Non-responders	Persistent	4 (9.5%)	5 (11.9%)	

Data are presented as numbers; percentages are in parenthesis

Both therapeutic regimens significantly (p<0.001) reduced the duration of blood loss compared to baseline duration of blood loss with significant reduction at 6-m compared to 3-m. LNG-IUS significantly (p=0.003) reduced duration of blood loss at both 3- and 6-months after insertion compared to oral therapy, (Fig. 2). Moreover, the heaviness of vaginal bleeding as judged by pictorial blood loss assessment chart showed significantly reduced amount of bleeding at 3-m, in both groups, compared to baseline amount with significant reduction at 6-months compared to amount recorded at 3-m in group L, while the difference was non-significant in group O. amount of vaginal bleeding was significantly low at 3-m and 6-m in group L compared to group O, despite the non-significant difference at baseline, (Table 3, Fig. 3).

Table (3): Duration and heaviness of vaginal bleeding data determined at the end of 3- and 6- months in both groups compared to baseline data

			Baseline	3-m	6-m
Duration of bleeding (days)	Group O	Mean	7.7±1 (6-10)	3±1 (2-5)	1.8±0.8 (1-3)
		P_1		<0.001	<0.001
		P_2			<0.001
	Group L	Mean	7.6±1 (6-9)	2.5±0.7 (1-4)	1.4±0.5 (1-2)
		P_1		<0.001	<0.001
		P_2			<0.001
		P_3	>0.05	=0.003	=0.003
Heaviness of vaginal bleeding (Mean score on pictorial blood assessment chart)		Group O	24.5±15.6	12.9±15.2	8.4±13.4
		P_1		<0.001	<0.001
		P_2			>0.05
		Group L	25.5±16.5	9.4±12.6	7.5±10.9
		P_1		<0.001	<0.001
		P_2			=0.001
		P_3	>0.05	=0.001	=0.026

Data are presented as mean±SD & numbers; ranges & percentages are in parenthesis; P_1: significance versus baseline duration; P_2: significance versus 3-m duration; P_3: significance versus Group O.

Mean duration of follow-up was 15.3±4.2; range: 7-24 months, without significance difference between both studied groups. Throughout follow-up duration, no case showed progression to atypical EH or carcinoma. At the end of follow-up, 42 patients found the used regimens excellent, 21 patients found

it very good and 16 patients found it good. However, in group O, 3 found oral therapy fair and two patients found it poor. The frequency of higher satisfaction rates was significantly (X^2=3.188, p<0.05) higher in group L compared to group O with significantly higher satisfaction scores by local therapy compared to oral therapy, (Table 4, Fig. 4).

Table (4): Patients' satisfaction scoring at end of 6- months of therapy determined in both groups

		Group O	Group L
Differential scores	Excellent	17 (40.5%)	25 (59.5%)
	Very good	11 (26.2%)	10 (23.8%)
	Good	9 (21.4%)	7 (16.7%)
	Fair	3 (7.1%)	0
	Poor	2 (4.8%)	0
	P_3		<0.05
Total score	Mean	3.9±1.2	4.4±0.8
	P_3		P<0.001

Data are presented as mean±SD & numbers & percentages are in parenthesis; P_3: significance versus Group O.

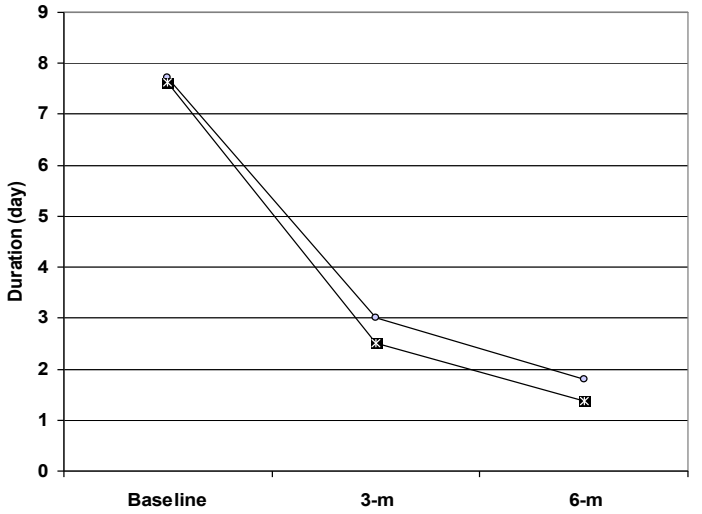

Fig. (2): Mean duration of vaginal bleeding recorded at the end of 6-months of follow-up

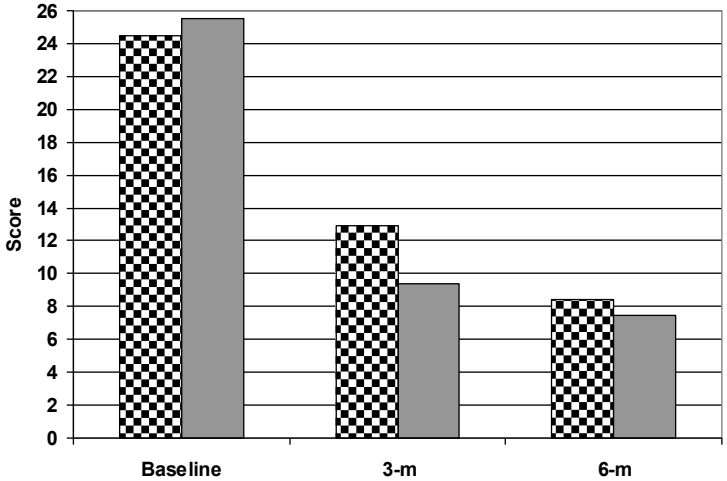

Fig. (3): Mean of pictorial blood assessment score reported of studied patients till end of 6-months therapy

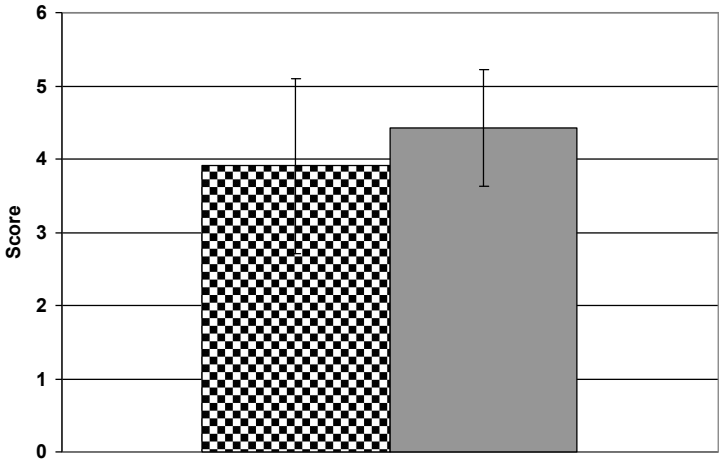

Fig. (4): Mean (±SD) satisfaction score of patients of both groups determined at the end of 6 months therapy

4. Discussion

Therapeutic outcome of the use of progestins for management of women presented with AUB and had biopsy-confirmed SEH was bi-armed subjectively as its effect on AUB and objectively as the histological response to therapeutic modality used. The significantly higher control of bleeding reported in group L compared to group O indicated the beneficial effects of LNG-IUS as a sole therapeutic modality for management of AUB. In line with these data; ***Kriplani et al.*** [16] reported 77.7% and 100% cure rate at 3 and 36 months using LNG-IUS with a significant decrease in the mean number of bleeding days and pictorial blood loss assessment chart score at 1 month, and the decrease continued with treatment duration. ***Endrikat et al.*** [17] compared the efficacy of LNG-IUS versus combined oral contraceptives for treatment of menorrhagia and reported that in LNG-IUS group 80% of subjects had treatment success compared with 36.8 % with oral therapy with significantly lower menorrhagia severity score in the LNG-IUS group at all study time points. ***Bednarek & Jensen*** [18] reported that most LNG-IUS users for menorrhagia experienced a dramatic reduction in menstrual bleeding.

Objectively, the 3-months LNG-IUS histological response rate was 73.8% with significantly higher frequency of responders compared to NET (57.1%). These figures go in hand with that previously reported in literature; **Haoula *et al.*** [19] reported 87.5% and 84.2%, 12-month regression rates of EH without and with atypia, respectively. **Heikinheimo & Gemzell-Danielsson** [20] documented that LNG-IUS is equal or superior to treatment of EH, including atypical EH, with systemic progestins. **Kaunitz & Inki** [21] found LNG-IUS has a positive effect on most quality-of-life domains comparable to those achieved with hysterectomy or endometrial ablation, and is consistently a cost-effective option for women with heavy uterine bleeding (HUB) including those with underlying organic pathology or bleeding disorders. **Ewies & Alfhaily** [22] reported that LNG-IUS has been successfully used to treat EH without cytological atypia and selected cases of atypical EH and additionally there is strong evidence from randomized controlled trials that LNG-IUS prevents the development of EH in exogenous estrogen users.

Recently, **Abu-Hashim *et al.*** [23] found a significantly higher 3-month regression rate with LNG-IUS compared to NET; 67.8% vs. 47.5% for non-atypical EH in perimenopausal women. **Ismail *et al.*** [24] evaluated the efficacy of 3 progestin treatment regimens; medroxyprogesterone acetate (MPA), NET or insertion of LNG-IUS in the management of SEH without atypia in premenopausal women and found that patients in the LNG-IUS group showed the highest resolution rate (66.67%), while the resolution rate was 36.66% and 40% in MPA and NET groups, respectively.

Considering hysterectomy as the final line of management for non-responder to conservative therapy, at the end of 3-m trial, 29 patients were borne to have hysterectomy for a rate of 34.5%. However, on reciprocal use of progestin regimen, the response rate was 72.2% in patients received LNG-IUS compared to 63.6% in patients received NET therapy. Thus, at the end of 6-m study period, only 9 patients required hysterectomy for a frequency of 10.5%. These data indicated the beneficial effect of continuing conservative therapy for another season and change of the therapeutic program allowed

further reduction of number of hysterectomies performed to about one-third.

The reported final figure of hysterectomy coincided with that previously reported by **Bahamondes *et al.*** [25] who reported that both hysterectomy and LNG-IUS were effective in treatment of heavy uterine bleeding with fewer complications with LNG-IUS and concluded that LNG-IUS represents a good strategy for reducing the number of hysterectomies (14.5%) and the resources required for women with heavy uterine bleeding.

Interestingly, throughout the follow period, none of non-responders progressed to atypical EH, a finding pointing to a probability of prophylactic effect of the used regimen against progression of simple to atypical EH and so could provide prophylaxis against progression to carcinoma. In support of this assumption; **Morelli *et al.*** [26] evaluated the efficacy of LNG-IUS insertion in preventing atypical EH and endometrial cancer in symptomatic postmenopausal women and found that at 36 months, 91% of patients showed no recurrence of AUB with a significant reduction in the mean endometrial thickness and histologic regression of EH was observed in 79.4% and 97.5% cases at 12 and 36 months, respectively. Moreover, **Morelli *et al.*** [26] found that none of studied women in which EH persisted, reported cellular atypia or cancer progression at 12 and 36 months of follow-up and concluded that LNG-IUS represents an effective treatment option to manage postmenopausal women affected by AUB and EH and seems to be able to prevent the onset of atypical EH and endometrial cancer.

As another support for the prophylactic effect of LNG-IUS; **Pashov *et al.*** [27] treated 13 women with atypical EH with the combination of gonadotropin-releasing hormone agonist and LNG-IUS and found this type of therapy was effective for all these patients and may be offered to be used as an alternative to surgery in women with atypical EH or early stage 1A well-differentiated endometrial cancer in women of reproductive age.

It could be concluded that LNG-IUS is safe and efficient therapeutic modality for SEH in women with AUB. LNG-IUS significantly reduced hysterectomy rate and duration and severity of bleeding with high satisfaction rates. LNG-IUS could be used as prophylactic therapy as no patient progressed to atypia or cancer.

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