

Original Article

Long-Term Effects of Levonorgestrel IUD on Endometrial Pathology in Women with Heavy Menstrual Bleeding

Sadia Khan¹, Kulsoom Iqbal², Mah Rukh³

^{1,2}Postgraduate Resident Gyne & Obs, Hayatabad Medical Complex Peshawar

³Women Medical Officer, RHC Regi, Peshawar

Correspondence: Dr. Kulsoom Iqbal

Postgraduate Resident Gyne & Obs, Hayatabad Medical Complex Peshawar

kulsoom41400@gmail.com

Abstract

Objectives: To assess the long-term effects of LNG-IUD on endometrial pathology in women's presenting with heavy menstrual blood loss (HMB).

Methodology: This prospective experimental study was conducted from February 2023 to January 2024, in the Gynecology Department of Hayatabad Medical Complex, Peshawar. A total of 180 women diagnosed with menorrhagia were enrolled in the study. All insertions were performed under aseptic conditions by experienced gynecologists with at least five years of clinical expertise. Baseline demographic and clinical data were recorded, and all patients underwent Pipelle endometrial sampling before LNG-IUD insertion to assess histology. Patients were evaluated pre-insertion and again at the end of the study (12 months post-insertion).

Results: Of the 162 women completing the study, the mean Pictorial Blood Loss Assessment Chart (PBAC) score significantly decreased from 312.6 ± 51.7 to 84.3 ± 29.8 ($p < 0.001$), and hemoglobin levels increased from 9.4 ± 1.2 g/dL to 12.3 ± 1.1 g/dL ($p < 0.001$). Histopathological changes included glandular atrophy (79%), stromal decidualization (95%), and vascular remodeling (87%), with no significant increase in hyperplasia or atypia ($p = 0.68$). Adverse events were minimal, with cramping (12%) and irregular spotting (9%) being the most common.

Conclusion: LNG-IUD is a highly effective and safe treatment for menorrhagia, significantly reducing menstrual blood loss, improving anemia, and inducing favorable endometrial changes without increasing the risk of atypia.

Keywords: LNG-IUD, Endometrial pathology, PBAC score, Anemia, Histopathological changes.

Cite this article as: Khan S, Iqbal K, Rukh M. Long-Term Effects of Levonorgestrel IUD on Endometrial Pathology in Women with Heavy Menstrual Bleeding. *J Soc Obstet Gynaecol Pak.* 2025;15(2): 130-134. DOI. 10.71104/jsogp.v15i2.908

Introduction

Heavy menstrual bleeding (HMB) is defined as excessive menstrual blood loss of 80 mL or more per menstrual cycle, or bleeding that lasts longer than 7 days, which adversely affects a woman's physical, emotional, and social well-being.^{1,2} It affects 10–30% of reproductive-age women and significantly impairs their quality of life.³ HMB can lead to complications such as anemia, fatigue, and a reduced ability to perform daily activities.⁴ It affects 10–30% of women of reproductive age³, and this results in a considerable reduction in quality of life. HMB may lead to anemia and fatigue, and decreased activities of daily living.⁴ It may stem from a range of causes including hormonal imbalance, problems with hemostasis, and structural disorders such as uterine fibroids and polyps.⁵ Persistent unresolved

issues relating to treatment of gynecological HMB and a lack of understanding of the pathophysiology underlying this disorder and treatment response sustainability over time, would suggest the need for an expansion in this area.

The Levonorgestrel IUD effectively treats menorrhagia, especially when it occurs as a result of dysfunctional uterine bleeding (DUB). Although the LNG-IUD was initially introduced as a contraceptive method, recent research indicates that it also has considerable hemostatic properties, resulting in a significant reduction of menstrual blood loss (MBL), amelioration of anemia, and enhancement of quality of life.^{5, 6} Levonorgestrel acts by inducing endometrial atrophy, decreasing vascular proliferation, and suppressing endometrial

Authorship Contribution: ^{1,2}Substantial contributions to the conception or design of the work or the acquisition, analysis, ³Drafting the work or revising it critically for important intellectual content.

Funding Source: none

Conflict of Interest: none

Received: Feb 06, 2025

Accepted: April 14, 2025

growth which reveals its site of action therapeutic effects.⁷

As an example, the LNG-IUD has been shown to have an effectiveness comparable to that of surgical interventions like endometrial ablation and hysterectomy, thereby offering a more conservative, but still highly effective, long-term option for the management of menorrhagia.⁸ The LNG-IUD has also been shown to improve anemia and decrease menstrual blood loss, however, there is insufficient data to evaluate the potential of this device to cause reversible histopathologic changes like stromal fibrosis or vascular remodelling.⁹ Affecting symptomatic treatment aside, these changes could influence the long-term risk of endometrial hyperplasia or carcinoma with prolonged therapy.

Fewer studies have examined the endometrium histology, particularly in the long-term of women who are diagnosed with menorrhagia, despite the fact that many have focused on the use of LNG-IUD for the treatment of MBL and improvement of anemia. While some literature highlights glandular atrophy, stromal decidualization, and vascular remodeling, the extent and clinical relevance of these changes remains under-explored, especially in terms of the long-term implications and the potential risk of endometrial hyperplasia or carcinoma.¹⁰ This study provides an integrated view of the clinical and histopathological results in the histological assessment, covering both quantitative components (e.g., assessment of menstrual blood loss in the context of PBAC scores and hemoglobin levels) and the qualitative light microscopic analysis of endometrial tissue, in contrast to most previous work that has concentrated on the symptomatic approach to treatment. Such an approach provides a basis for more thorough chronic management counseling. Additionally, it offers a valid reason for assessing the effect of the LNG-IUD from the perspective of endometrial pathological changes.

Methodology

This was a prospective experimental study over 12 months' duration from the 1st February 2023 to 31st January 2024 in the Gynecology Department of Hayatabad Medical Complex, Peshawar. The study was approved by the Institutional Review Board of the institution. All patients were enrolled after signing written informed consent. Study Flow: Among 180 women, 162 completed the study and 18 were lost to follow-up (10%

attrition; Figure 1). Diagnosis of Heavy Menstrual Bleeding (HMB), defined as:

1. Patient-reported symptoms: Women reporting menstrual blood loss of > 80 mL for at least one cycle (based on a PBAC score > 100) or bleeding that lasted longer than 7 days.
2. Clinical diagnosis: the diagnosis of the heavy menstrual bleeding (HMB) was determined based on detailed clinical history, including the impact on daily activities, and physical examination to exclude other causes for abnormal uterine bleed.
3. Laboratory findings: A hemoglobin level of <10 gm/dL, or symptomatic iron deficiency anemia.
4. Imaging modalities: This may be a transvaginal ultrasonography (TVS) or hysteroscopic ultrasound (HSG), to check and confirm if there is any structural irregularity such as fibroids, polyps or adenomyosis.

The study eligibility stipulations included: participants who were in the age bracket of 25 to 50 years, had heavy menstrual bleeding, a uterus size over 12 weeks of gestational age confirmed by TVS, no history of LNG IUD, no endometrial hyperplasia, carcinoma or other malignancies, and willingness to consent to the study and follow up. The presence of pregnancy or lactation at the point of randomization, systemic diseases or coagulopathies which could influence the menstrual bleeding, hormonal treatment other than the LNG IUD which was being used at the time of randomization, structural uterine anomalies such as fibroid, polyp or adenomyosis and ultrasound, and excessive uterine size (>12 weeks of gestation as assessed by transvaginal sonography) were considered to be criteria for exclusion together with the contraindications for the use of the LNG IUD which included active pelvic inflammatory disease, current or recent genital tract infection, or a uterine anomaly of congenital type.

Senior gynecologists with years of experience in this procedure performed the LNG-IUD insertions on every participant in accordance with aseptic measures for uniformity. In order to rule out pregnancy, it was carried out during the first five days of the menstrual cycle. During the study period, iron supplements were used as needed for anemia, but no other oral medication (such as tranexamic acid or oral contraceptives) was prescribed. At each three-month follow-up visit, menstrual blood loss (MBL) was assessed using the PBAC score, and the amount of time needed to achieve

a clinically meaningful MBL reduction was noted and examined.

Basic demographic and clinical data were recorded on a pre designed proforma including age, BMI, menstruation history, and any treatment history of HMB. A Pipelle endometrial sample was collected from each woman to provide a baseline histology before the LNG-IUD was implanted.

Patients were followed up periodically at 3-month intervals. Patient-reported outcomes were assessed at each visit, including the PBAC score to measure menstrual blood loss (MBL), hemoglobin levels, and side effects. Menstrual blood loss (MBL) was assessed using the Pictorial Blood Loss Assessment Chart (PBAC). Patients were provided with a standardized chart and instructed to record the number of sanitary products (pads or tampons) used during their menstrual cycle, along with the degree of soiling (lightly soiled = 1 point, moderately soiled = 5 points, fully soiled = 20 points). Small clots were assigned 1 point, and large clots were assigned 5 points. The total PBAC score was calculated by summing the points for all products used during the cycle. A PBAC score >100 was considered indicative of heavy menstrual bleeding (HMB). Side effects monitored included irregular bleeding or spotting, amenorrhea, breast tenderness, mood changes, headaches, pelvic pain, LNG-IUD expulsion, weight changes, acne, and signs of infection (e.g., fever or abnormal discharge). Additionally, symptoms of anemia (such as fatigue, dizziness, and shortness of breath) and general well-being were evaluated to provide a comprehensive understanding of the patients' health status and quality of life.

The participants who underwent LNG-IUD insertion for one year had another endometrial biopsy to determine histopathological alterations. Endometrial biopsies were performed using the Pipelle biopsy method, a minimally invasive technique for obtaining endometrial tissue samples. All biopsy samples were handled, sectioned, and analyzed by expert histopathologists who were blinded to the patients' clinical information. Histological patterns assessed included glandular atrophy, stromal decidualization, vascularity (density and distribution of blood vessels), and the presence or absence of hyperplasia or atypia.

Statistical analysis of the data was conducted using SPSS, the version used here was 26. Continuous data were presented using mean \pm SD while categorical data were displayed using frequencies with percentages, for

baseline characteristics. Independent samples t-tests were conducted to compare the differences in the mean pre- and post-intervention hemoglobin levels and PBAC scores. Histopathological changes were described using McNemar's test, for paired categorical data. Statistical significance was set at p-value of <0.05.

Results

The mean age of participants was 34.5 ± 8.1 years, and the mean BMI was 25.3 ± 3.7 kg/m². Baseline characteristics are summarized in Table I.

Table I: Baseline Characteristics of Study Participants.

Characteristic	Mean \pm SD
Age (years)	34.5 \pm 8.1
BMI (kg/m ²)	25.3 \pm 3.7
	n (%)
Parity (n): 0	21 (13%)
Parity (n): 1–3	96 (59%)
Parity (n): >3	45 (28%)
Mean Hemoglobin (g/dL)	9.4 \pm 1.2
Mean PBAC Score	312.6 \pm 51.7

A significant reduction in menstrual blood loss was observed after 12 months of LNG-IUD use. The mean PBAC score significantly decreased from 312.6 ± 51.7 at baseline to 84.3 ± 29.8 , with a mean reduction of 228.3 ± 56.2 ($p < 0.001$). Table II

Table II: Comparison of PBAC Scores and Hemoglobin Levels.

Parameter	Baseline	After 12 Months	p-value
PBAC Score	312.6 \pm 51.7	84.3 \pm 29.8	<0.001
Hemoglobin (g/dL)	9.4 \pm 1.2	12.3 \pm 1.1	<0.001

Repeat endometrial biopsy showed significant histopathological alterations after LNG-IUD use. At baseline, all endometrial biopsies were consistent with normal proliferative or secretory endometrium, with no evidence of glandular atrophy, stromal decidualization, or vascular remodeling. Hyperplasia or atypia was observed in 4 (2.5%) cases at baseline, which resolved in 2 cases after 12 months of LNG-IUD use. Table III

Table III: Histopathological Findings Pre- and Post-LNG-IUD Use.

Histological Parameter	Baseline n (%)	After 12 Months n (%)	p-value
Glandular Atrophy	0 (0%)	128 (79%)	<0.001
Stromal Decidualization	0 (0%)	154 (95%)	<0.001
Vascular Remodeling	0 (0%)	141 (87%)	<0.001
Hyperplasia or Atypia	4 (2.5%)	2 (1.2%)	0.68

Table IV: Adverse Events Following LNG-IUD Insertion.

Adverse Event	% of Total Participants (n = 162)	% of Adverse Event Cases (n = 37)	Time of Occurrence (Post-Insertion)
Cramping	12% (n = 19)	52.2%	Mostly within the first 3 months
Irregular Spotting	9% (n = 15)	39.1%	Mostly within the first 3 months
LNG-IUD Expulsion	2% (n = 3)	8.7%	Within the first 3 months
Severe Complications	0% (n = 0)	0%	N/A
Device-Related Infections	0% (n = 0)	0%	N/A

Adverse events were observed in 23% (n = 37) of patients, primarily within the first three months post-insertion. Among these, the most commonly reported were cramping (52.2% of adverse event cases, 12% of total study participants), irregular spotting (39.1% of adverse event cases, 9% of total participants), and LNG-IUD expulsion (8.7% of adverse event cases, 2% of total participants). No cases of severe complications or device-related infections were reported throughout the study period. (Table IV)

Discussion

The results of this study support the effectiveness of LNG-IUD regarding the management of heavy menstrual bleeding (HMB) during the follow up period as well as the decrease in menstrual blood loss and marked histopathological changes on the endometrium. After one year of LNG-IUD use, the mean PBAC score had a considerable reduction from 312.6 ± 51.7 pre-insertion to 84.3 ± 29.8 post-insertion ($p < 0.001$) which was comparable with earlier studies where LNG-IUD has been reported to reduce MBL by 80–90%.^{11,12}

Mean hemoglobin increased significantly from 9.4 ± 1.2 g/dL at baseline to 12.3 ± 1.1 g/dL at 12 months follow up ($p < 0.001$); hence, confirming the effectiveness of LNG-IUD in the management of menorrhagia induced anemia. This result supports previous findings about the impact of LNG-IUD use in addressing anemia and the improvement of the quality of life.¹³

Histopathological analysis revealed significant endometrial changes, including glandular atrophy (79%), stromal decidualization (95%), and vascular remodeling (87%). These findings correlate with Kavasoglu A et al and Malik F et al literature for the local effect of levonorgestrel on endometrial tissue where cellular proliferation is attenuated and the decidualization process is enhanced.^{14,15} Importantly, no significant hyperplasia or atypia were found which is reassuring of the risk of any negative endometrial changes after prolonged use as stated by Averbach S et al.¹⁶ Minor adverse effects of LNG-IUD were previously documented, and in this study, cramps (12%) and

irregular spotting (9%) were reported by some patients. These findings are in line with literature that describes these side effects as transient and mild. The low expulsion rate (2%) also illustrates LNG-IUD overall acceptability and retention rates within a larger community network.¹⁷

However, a number of key limitations are apparent despite the promising outcomes. Potential of LNG-IUD in long term use to control heavy menstrual bleeding and overall effect on long term reproductive potential remains largely unexplored even with strong evidence pertaining to the safe and effective short-term use of the device. Further follow-up beyond 12 months is required to ascertain if the advantages are sustained with no late complications. Also, this analysis was performed at a single institution, which may limit its generalizability. Our findings need to be validated in larger randomized multicentric trials of women studying women with comorbidities or the obese PCOS at risk of perimenopause.

In addition to excluding a significant proportion of menstruation patients, this study did not investigate typical, crucial aspects of patient-reported outcomes that have a significant influence on how well treatment is viewed, such as mood, sexuality, and menstrual discomfort. These beliefs should be considered when tailoring counselling and the LNG-IUD to enhance their acceptability and appropriateness to better meet the wide-ranging needs of women with HMB. In addition to improving knowledge of variations in relative efficacy, safety, and cost-effectiveness, head-to-head trials of LNG-IUD with other treatments (oral contraceptives, tranexamic acid, and endometrial ablation) should also sharpen the focus on best practice guidelines for LNG-IUD as a first-line therapy.

Conclusion

This study shows that LNG-IUD is effective and safe method of managing heavy menstrual bleeding (HMB) as results depicted a significant decrease in menstrual blood loss, an improvement in hemoglobin level and histopathological changes of the endometrium that

affects the quality of life of women. The results indicate that it could be developed as a first-line, definitive treatment for women seeking non-invasive and reversible management of heavy menstrual bleeding (HMB).

References

1. D'Alton ME, Rood KM, Smid MC, Simhan HN, Skupski DW, Subramaniam A, et al. Intrauterine vacuum-induced hemorrhage-control device for rapid treatment of postpartum hemorrhage. *Obstet Gynecol.* 2020;136(5):882-91. doi:10.1097/AOG.0000000000004138.
2. Hunter TA, Sonalkar S, Schreiber CA, Perriera LK, Sammel MD, Akers AY. Anticipated pain during intrauterine device insertion. *J Pediatr Adolesc Gynecol.* 2020;33(1):27-32. doi:10.1016/j.jpag.2019.09.007.
3. Evans AT, Szlachetka K, Thornburg LL. Ultrasound assessment of the intrauterine device. *Obstet Gynecol Clin North Am.* 2019;46(4):661-81. doi:10.1016/j.ogc.2019.07.005.
4. Zhao Q, Hongyan M. Efficacy of levonorgestrel intrauterine extended release system in the treatment of menorrhagia. *Womens Health Res.* 2020;10:58-9.
5. Tan J, Yong P, Bedaiwy MA. A critical review of recent advances in the diagnosis, classification, and management of uterine adenomyosis. *Curr Opin Obstet Gynecol.* 2019;31(4):212-21. doi:10.1097/GCO.0000000000000555.
6. Chen S, Liu J, Peng S, Zheng Y. LNG-IUS vs. medical treatments for women with heavy menstrual bleeding: A systematic review and meta-analysis. *Front Med (Lausanne).* 2022;9:948709. doi:10.3389/fmed.2022.948709.
7. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097.
8. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editors. *Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021).* Cochrane; 2021.
9. Schünemann HJ, Vist GE, Higgins JPT, Santesso N, Deeks JJ, Glasziou P, et al. Chapter 15: Interpreting results and drawing conclusions. In: Higgins JPT, Thomas J, Chandler J, et al, editors. *Cochrane Handbook for Systematic Reviews of Interventions version 6.2.* Cochrane; 2021.
10. Dong G. Clinical observation of menorrhagia treated with Mirena IUD. *Sci Regimen.* 2021;24:130-1. Available from: <https://d.wanfangdata.com.cn/periodical/kxys202101130>.
11. Bofill Rodriguez M, Lethaby A, Jordan V. Progestogen-releasing intrauterine systems for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2020;2020(4):CD002126. doi:10.1002/14651858.CD002126.pub4.
12. Rodriguez MB, Dias S, Jordan V, Lethaby A, Lensen SF, et al. Interventions for heavy menstrual bleeding; overview of cochrane reviews and network meta-analysis. *Cochrane Database Syst Rev.* 2022;2022(5):CD013180. doi:10.1002/14651858.CD013180.pub2.
13. Oderkerk TJ, van de Kar MMA, van der Zanden CHM, Geomini PMAJ, Herman MC, Bongers MY. The combined use of endometrial ablation or resection and levonorgestrel-releasing intrauterine system in women with heavy menstrual bleeding: a systematic review. *Acta Obstet Gynecol Scand.* 2021;100(10):1779-87. doi:10.1111/aogs.14219.
14. Kavasoglu A, Ahmet G. Progesterone treatment preference in heavy menstrual bleeding: Per Os or Levonorgestrel releasing intrauterine device. *Kuwait Med J.* 2020;52(1):29-35.
15. Malik F, Samankal S, Rukhsana K. Comparative trial of levonorgestrel intrauterine system and norethisterone for treatment of idiopathic menorrhagia. *Pakistan J. Medical Health Sci.* (2020) 14:1184–6.
16. Averbach SH, Ermias Y, Jeng G, Curtis KM, Whiteman MK, Berry-Bibee E, et al. Expulsion of intrauterine devices after postpartum placement by timing of placement, delivery type, and intrauterine device type: a systematic review and meta-analysis. *Am J Obstet Gynecol.* 2020;223(2):177-88. doi:10.1016/j.ajog.2020.02.045.
17. Exacoustos C, Zupi E. A new era in diagnosing adenomyosis is coming. *Fertil Steril.* 2018;110(5):858. doi:10.1016/j.fertnstert.2018.07.005.