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Original Research Article

Histopathological insights into treatment failure with the levonorgestrel releasing intrauterine system in women with heavy menstrual bleeding: a retrospective study

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ABSTRACT

Background: The levonorgestrel-releasing intrauterine system (LNG-IUS) is an established first-line therapy for heavy menstrual bleeding (HMB), effectively reducing menstrual blood loss and improving quality of life in most women. However, a subset of patients fails to achieve adequate response, warranting evaluation of potential underlying causes.
Methods: This retrospective study was conducted at BARC Hospital, Mumbai, from January 2017 to March 2020, and included 88 women with HMB treated with LNG-IUS. Non-responders were identified based on persistent heavy bleeding despite therapy. Endometrial biopsy and, where applicable, hysterectomy specimens were analyzed to determine histopathological findings associated with treatment failure.
Results: Of the 88 women treated, 26 (29.5%) were classified as non-responders. Endometrial biopsy revealed proliferative endometrium in 65.4%, disordered proliferative endometrium in 19.2%, and secretory endometrium in 15.4% of cases. Among nine non-responders who underwent hysterectomy, adenomyosis was the most common finding (44.4%), followed by adenomyosis with leiomyoma (33.3%), endometrial polyp (11.1%), and leiomyoma (11.1%).
Conclusions: Treatment failure of LNG-IUS in women with HMB was predominantly associated with structural uterine abnormalities, particularly adenomyosis. Comprehensive pre-insertion evaluation, including clinical and imaging assessment, is essential to detect underlying pathology and optimize patient selection. Individualized management based on uterine morphology and symptom profile may improve therapeutic success and reduce delays in achieving symptom control.

Keywords: Heavy menstrual bleeding, Levonorgestrel-releasing intrauterine system, Treatment failure, Adenomyosis, Leiomyoma, Endometrial pathology

INTRODUCTION

Heavy menstrual bleeding (HMB), defined as excessive menstrual blood loss that interferes with a woman's physical, emotional, social, and material quality of life, continues to be a significant gynecological issue worldwide. It accounts for a substantial proportion of outpatient visits and remains a leading indication for hysterectomy worldwide, despite the availability of effective medical therapies., This often leads to anemia, fatigue, impaired productivity, and reduced quality of life, thereby necessitating effective long-term therapeutic options.[1] The 52-mg levonorgestrel intrauterine system (LNG-IUS) has emerged as one of the most effective non-surgical treatments for HMB. Contemporary prospective studies have demonstrated that LNG-IUS significantly

reduces menstrual blood loss, improves hemoglobin and ferritin levels, and enhances overall quality of life in as early as three to six months of use.[2] A recent meta-analysis further confirmed that LNG-IUS provides superior bleeding control and higher treatment satisfaction compared to conventional medical therapies, reinforcing its role as a first-line intervention.[3]

Despite its proven efficacy, a notable subset of women continues to experience persistent heavy bleeding or inadequate clinical response after LNG-IUS insertion. Identifying underlying causes—such as occult adenomyosis or leiomyomas—is crucial to improving patient selection, counselling, and treatment outcomes. Against this background, the present study evaluates histopathological findings among women who failed to respond to LNG-IUS, aiming to elucidate factors contributing to treatment failure and guide more individualized management strategies.

METHODS

This retrospective study was conducted at Bhabha Atomic Research Centre Hospital, Mumbai between January 2017 and March 2020. A total of 88 women presenting with HMB who were treated with the levonorgestrel intrauterine system (LNG-IUS) were included. Patients with suspected endometrial or cervical malignancy, as well as those with contraindications to progesterone therapy or intrauterine device insertion, were excluded.

Treatment outcomes were assessed during follow-up, and patients who did not experience satisfactory improvement in symptoms were classified as non-responders. These women underwent further evaluation to determine the possible causes of treatment failure. Endometrial biopsy samples were obtained and subjected to histopathological examination. Patients who opted for surgical management underwent hysterectomy, and the excised specimens were analysed histopathologically.

The histopathological findings from both endometrial biopsy and hysterectomy specimens in non-responders were systematically recorded and evaluated to identify common pathological correlates of LNG-IUS failure.

Qualitative variables were presented as frequencies and percentages, and quantitative variables as mean ± standard deviation (SD). Independent samples *t*-test was used for quantitative data and Chi-square test for categorical data. A p value <0.05 was considered statistically significant.

RESULTS

A total of 88 patients underwent LNG-IUS insertion for the management of heavy menstrual bleeding. On follow-up, 26 patients (29.5%) were identified as non-responders.

Demographic characteristics of non-responders

A majority of non-responders were aged 40-49 years, also the most common age group for heavy menstrual bleeding.

Table 1: Age of non-responders.

Age (years)	Percentage (%)
35-39	15.3
40-44	30
45-49	30
50-54	7.7

Endometrial biopsy findings

Histopathological evaluation of endometrial biopsies from non-responders revealed that the majority had a proliferative endometrium (65.4%, n=17), while 19.2% (n=5) showed disordered proliferative endometrium, and 15.4% (n=4) had secretory endometrium (Table 1). These findings suggest that most treatment failures occurred in patients with a relatively normal or proliferative endometrial pattern, indicating that the cause of persistent bleeding may not be directly related to endometrial pathology alone.

Hysterectomy findings among non-responders

Among the 26 non-responders, 9 patients proceeded with hysterectomy. Histopathological examination of surgical specimens revealed adenomyosis in 44.4% (n=4), adenomyosis with leiomyoma in 33.3% (n=3), and endometrial polyp or leiomyoma in 11.1% each (n=1 each) (Table 2).

These results highlight that underlying structural abnormalities, particularly adenomyosis (alone or in combination with leiomyoma), were the predominant causes of treatment failure.

Table 2: Histopathological findings on endometrial biopsy.

Histopathological findings	Non-responders	Responders	Total	Percentage (%)
Proliferative	17	42	59	65.4
Disordered proliferative	5	7	11	19.2
Secretory	4	13	18	15.4

Table 3: Histopathological findings after hysterectomy in non-responders.

Histopathology	No. of patients	Percentage (%)
Adenomyosis	4	44.4
Adenomyosis with leiomyoma	3	33.3
Endometrial polyp	1	11.1
Leiomyoma	1	11.1
Total	9	

DISCUSSION

In our study, 88 women with HMB were treated with LNG-IUS, of whom 29.5% were non-responders. This non-responder rate is within the range reported in other studies, where discontinuation or failure rates have varied between 20–40% depending on follow-up duration and population characteristics.[6,7] For example, a Dutch cohort reported a continuation rate of 73% at 24 months, while an Indian series reported expulsion or discontinuation in nearly one-third of women at long-term follow-up.[8] Thus, our findings corroborate prior evidence that despite high efficacy overall, a substantial subset of women derive limited or no benefit from LNG-IUS. Histopathological analysis of endometrial biopsies among non-responders in our study revealed proliferative endometrium in 65.4% of cases, disordered proliferative endometrium in 19.2%, and secretory endometrium in 15.4%. These findings suggest that treatment failure was not primarily due to endometrial pathology but may relateto deeper structural abnormalities. Indeed, among women who proceeded to hysterectomy, adenomyosis was the most frequent finding (44.4%), either alone or combined with leiomyoma (33.3%). This aligns with previous reports highlighting adenomyosis and fibroids as common contributors to LNG-IUS failure.[5-10] Adenomyosis, in particular, has been consistently associated with suboptimal bleeding control and higher discontinuation rates.[11] While LNG-IUS can improve bleeding and pain in some patients with adenomyosis, its efficacy is often limited in those with extensive disease.[12]

Overall, this study supports existing literature that while LNG-IUS is highly effective for many women with HMB, a significant minority—particularly those with adenomyosis—may not achieve adequate symptom control.

CONCLUSION

This study demonstrates that while LNG-IUS is highly effective for many women with HMB, nearly one-third may fail to respond adequately, with adenomyosis emerging as a predominant underlying factor. Careful pre-insertion evaluation to detect structural uterine pathology, particularly adenomyosis and leiomyomas, can improve patient selection, optimise outcomes, and reduce unnecessary delays in achieving effective symptom control. Our findings highlight the need for patient-tailored management strategies and support future prospective studies exploring predictors of non-response and the role of alternative medical therapies in this subgroup.

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