Real-world Safety and Effectiveness Analysis of Norethisterone in the Management of Abnormal Uterine Bleeding

Arun Madhab Boruah¹, Pushpa Jaiswal², Monika Chinda³, Ashok Jaiswal⁴

Abstract
Objective: To assess the real-world safety and effectiveness of norethisterone 10 mg-controlled release (CR) formulation in the management of abnormal uterine bleeding (AUB).

Methods: This was a retrospective analysis of real-world data collected between January 2021 and March 2021 across 40 centers in India. A total of 308 women in the reproductive age-group (18–45 years) with ovulatory AUB were treated with norethisterone CR 10 mg once a day for 10 days. The data from women with a confirmed diagnosis of AUB were included in the study. The clinical records that were analyzed for the primary objectives included the time required for arresting heavy menstrual bleeding after initiating medication, the incidence of breakthrough bleeding, safety and tolerability, and the secondary objectives included the timing of withdrawal bleeding after the last tablet was taken, assessment of heaviness of bleeding, and treatment compliance.

Results: The mean age (± standard deviation (SD)) was 33.8 ± 8.3 years. Out of the 308 women with AUB, the majority of women (n = 193, 63%) experienced styptic action of norethisterone 10 mg CR within 4 hours of administration of the medication, 61% of the women (n = 187) did not report any incidence of breakthrough bleeding, and 70% of the women (n = 216) reported withdrawal bleeding within 24–72 hours of administration of the last medication dose. No adverse events were reported. Heavy bleeding was noted in only 7% of the women. More than 80% of compliance with therapy was observed in 94% of women (n = 290).

Conclusion: Our analyses of the retrospective data suggested that norethisterone 10 mg CR was safe and effective for the treatment of AUB in Indian women.

Clinical significance: To the best of our knowledge, this is the first real-world study to show that norethisterone 10 mg CR effectively treats AUB, is safe, and is associated with a high compliance rate in Indian women of reproductive age-group (18–45 years).

Keywords: Abnormal uterine bleeding, Breakthrough bleeding, Compliance, Norethisterone, Oral progesterone, Safety.

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Introduction
Abnormal uterine bleeding (AUB) is defined as any type of uterine bleeding in which the amount, duration, or frequency is excessive for the patient, and is not attributed to any detectable systemic or uterine pathology, or pregnancy.¹,² The signs of AUB include heavy menstrual bleeding (above 95th centile of the normal population), heavy and prolonged menstrual bleeding, and intermenstrual bleeding.³ AUB negatively affects the emotional, physical, sexual, and professional lives of women, thereby worsening their quality of life.⁴ It is a common complaint affecting a large number of women from menarche to menopause.⁵ The prevalence of AUB varies from 3% to 30% among women in the reproductive age-group.⁶ In Indian women, the prevalence of AUB ranges from 17.9% to 32.72%.¹,²

The International Federation of Gynecology and Obstetrics (FIGO) has provided an acronym, polyps, adenomyosis, leiomyoma, malignancy–coagulopathies, ovulatory dysfunction, endometrial, iatrogenic, and not otherwise classified (PALM-COEIN) to categorize the causes of AUB.⁷ The available treatment strategies for AUB aim to lower the volume of bleeding and prevention of its recurrence. Some of these include antifibrinolytic agents, nonsteroidal anti-inflammatory drugs, progesterone, combined oral contraceptive pills, and gonadotropin-releasing hormone analogs. The choice of the treatment strategy is based on the cause of the disorder.² Surgical treatment may be necessary in case of severe and prolonged bleeding.³

Among the oral progesterone, norethisterone is most commonly used in the treatment of AUB.⁸ Norethisterone acts by suppressing endometrial development through antiproliferative endometrial effect, thereby correcting unpredictable bleeding patterns and reducing menstrual flow.⁵,¹⁰ It is used in about 38% of the AUB patient population, owing to minimal side effects and cost-effectiveness.¹⁰ Norethisterone is commonly prescribed at a dosage of 5 mg thrice daily from day 5 to day 26 of the menstrual
Real-world Analysis of Norethisterone in AUB

The dose varies between 10 and 15 mg/day, according to the indication. This therapeutic regimen has been shown to lower blood loss by >80%. In the present study, we determined the real-world safety and effectiveness of the conservative management of AUB with norethisterone 10 mg CR formulation in a real-world scenario.

METHODS

Study Design and Participants
This was a real-world study involving a retrospective analysis of data collected from the outpatient departments (OPDs) of 40 centers across India between January 2021 and March 2021. The data related to women in the reproductive age-group (18–45 years) diagnosed with AUB and managed with norethisterone CR 10 mg once a day for 10 days were evaluated.

Aims and Objectives
This retrospective study was performed to assess the real-world safety and effectiveness of norethisterone 10 mg CR in the management of AUB. The aims and objectives were as follows:

- Evaluate the safety of norethisterone 10 mg CR based on the adverse events reported during the therapy.
- Evaluate the effectiveness of norethisterone 10 mg CR in the management of AUB.
- Assess the incidence of breakthrough bleeding while on therapy.
- Assess the heaviness of bleeding and patient compliance.

Data Collection
The clinical records from the OPDs were analyzed for parameters such as time required to arrest heavy bleeding after the initiation of medication, heaviness of the bleeding, incidence of breakthrough bleeding while on treatment, time of withdrawal bleeding after the last tablet was taken, compliance and tolerability to the treatment, and any adverse event noted during the treatment. Data on demographics and vital signs were also obtained from the clinical records.

Statistical Analysis
Categorical variables are presented as numbers and percentages, and continuous data as mean and standard deviation.

RESULTS

Baseline Characteristics
Data from medical records of 308 eligible women diagnosed with AUB between January 2021 and March 2021 were evaluated. The mean age of the study population was 33.8 years with a mean duration of illness of 8.7 months. Intermenstrual bleeding was present in about one-third of patients (36%). The mean age of menarche was 13.1 years. The baseline clinical characteristics are summarized in Table 1.

Safety
No adverse events were reported during the treatment period. The treatment was found to be well-tolerated.

Effectiveness
The primary objectives considered for evaluating the effectiveness of norethisterone 10 mg CR included the timing of styptic action and incidences of breakthrough bleeding. Styptic action was noted within 4 hours in the majority of the study population (63%, n = 193), while it was noted at 5–6 hours and >6 hours among 21% (n = 64) and 16% (n = 51) of the population, respectively (Fig. 1).

Incidence of Breakthrough Bleeding
The majority of the population (61%, n = 187) did not report any incidence of breakthrough bleeding, while 27% (n = 85) and 12% (n = 36) of women noted breakthrough bleeding for 1–2 days and ≥3 days, respectively (Fig. 2).

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Age (years) (N = 307) (mean ± SD)</th>
<th>33.8 ± 8.3</th>
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<tr>
<td></td>
<td>Duration of Illness (N = 281) (months) (mean ± SD)</td>
<td>8.7 ± 15.3</td>
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<td></td>
<td>SBP (N = 302) mm Hg (mean ± SD)</td>
<td>121.3 ± 12.3</td>
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<tr>
<td></td>
<td>DBP (N = 298) mm Hg (mean ± SD)</td>
<td>77.6 ± 8.7</td>
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<tr>
<td></td>
<td>Intermenstrual bleeding n (%)</td>
<td>111 (36)</td>
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<tr>
<td></td>
<td>Postcoital bleeding n (%)</td>
<td>25 (8)</td>
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<tr>
<td></td>
<td>Age of menarche (N = 262) (mean ± SD) in years</td>
<td>13.1 ± 1.5</td>
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<td></td>
<td>DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation</td>
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Fig. 1: Timing of styptic action (N = 308)

Fig. 2: Incidences of breakthrough bleeding (N = 308)
Patient Compliance and Other Secondary Objectives

The timing of the withdrawal bleeding after the last tablet was taken and their compliance with the treatment were considered as secondary objectives. In the majority of the study population (70%, n = 216), the timing of withdrawal bleeding after the last dose of norethisterone 10 mg CR was 24–72 hours (Table 2). Treatment compliance was >80% among 94% (n = 290) of women included in the analysis (Table 2).

In addition, the secondary objective also included the analysis of the heaviness of bleeding, which has been presented in Figure 3. Out of the 241 women analyzed, a majority (59%, n = 142) reported using ≤6 pads/day.

Discussion

In the present retrospective real-world analysis, norethisterone 10 mg CR formulation was able to exert its action within 4 hours of administration in the majority of the patients (63%), with no incidence of breakthrough bleeding in 61% of patients. None of the participants reported any adverse event, and their compliance with the therapy was high.

The mean age of the study participants was 33.8 years, which aligned with a similar Indian study assessing the effectiveness of norethisterone in the management of AUB.12 Other studies have reported a relatively higher mean age of women with AUB, ranging from 36 to 39 years.10,17,14 This could be explained by the better health status of younger women as compared to women in later years of life.10 The mean duration of symptoms was high (about 8.7 months). Other studies from the Indian setting have also reported a high mean duration of AUB, which could be possibly explained by general neglect and late presentation to the hospital.10,13

Since a significant proportion of Indian women experience AUB, which negatively affects their quality of life, evidence-based first-line treatment is commonly prescribed by general practitioners.2 The Gynae Endocrine Society of India (GESI) recommends norethisterone cyclically (for 21 days) as first-line therapy in acute episodes of bleeding associated with ovulatory AUB for 3 months.15 Although the exact underlying cause of AUB still lacks clarity, progesterone-associated morphological and functional changes in the endometrium are frequently observed among women presenting with AUB. Maintenance of a sustained level of progesterone helps to normalize the level of menstrual bleeding.2 The present real-world study in addition to other reports establishes the effectiveness of norethisterone in the management of AUB.2,12,16 Even in women with warfarin-induced AUB, 5 mg thrice-daily dose of norethisterone effectively and safely controls AUB.17 Further, a doctor-centric survey from India revealed that 43.85% of physicians prescribe hormonal therapy for the management of AUB.1

In a study by Taneja et al., AUB symptoms were completely resolved in 56.7% of women after a three-week course of twice-daily 10 mg norethisterone.12 Norethisterone is considered an effective and reliable treatment option for AUB among adolescents.18 A retrospective study on adolescent women aged <21 years showed that 5–10 mg/day of norethisterone suppressed menstrual bleeding in 83% of women with a bleeding disorder.19 Norethisterone is reported to be more effective and better tolerated in the management of puberty menorrhagia as compared to combined oral contraceptive pills.15 In our study, styptic action was noted in ≤4 hours for the majority of the study population. Studies have shown that as compared to oral norethisterone, the levonorgestrel-containing intrauterine device (IUD) is better for the treatment of chronic AUB.20 However, the acceptance of IUDs is still poor and there is a higher preference for oral AUB medications, owing to lesser side effects.2

Norethisterone is equally effective as a combined oral contraceptive in the treatment of AUB.2 Here, we found that the majority of the population did not report heavy menstrual bleeding and 59% of women reported using ≤6 pads/day. Further, 61% of the women did not experience any incidence of breakthrough bleeding.

The adverse effects associated with norethisterone are irregular menstrual bleeding, acne, hirsutism, weight gain, nausea, spotting, gastritis, abdominal discomfort, and headache.2,10,21 However, norethisterone is not associated with major side effects.12,13,22 Interestingly, in the present study, norethisterone was not associated with any adverse event, which could be possibly explained by the once-daily CR formulation and short duration of treatment (10 days). The good safety profile of the treatment was reflected as a high compliance rate among 94% of the women with AUB receiving norethisterone 10 mg CR. Another randomized controlled study reported that the satisfaction rate was 70% with norethisterone in heavy menstrual bleeding.23

Strengths and Limitations

The strength of the present study is that it included participants from different centers spanning various states of India. Another strength of the study was the good sample size. Therefore, the findings may present an overall view of the norethisterone treatment response in Indian women. However, the major limitation of the study was that the treatment response (both safety and effectiveness) was based on the report of the patients; therefore,

<table>
<thead>
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<th>Table 2: Secondary objectives (N = 308)</th>
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<tr>
<td><strong>Timing of withdrawal bleeding after administration of last norethisterone tablet</strong></td>
</tr>
<tr>
<td>24–72 hours</td>
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<tr>
<td>More than 72 hours</td>
</tr>
<tr>
<td><strong>Percentage of compliance to therapy</strong></td>
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<tr>
<td>More than 80%</td>
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<tr>
<td>Less than 80%</td>
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Fig. 3: Heaviness of bleeding in terms of the number of pads used (%; N = 241)
the possibility of any error in reporting cannot be completely ruled out. Further, as the study involved retrospective data collection, there was a possibility of missing or unavailability of some data. For example, data on certain specific criteria like the presence of dysmenorrhea, and irregularities in menstrual cycles at baseline and after treatment, were not available. A long-term follow-up of the study participants to assess the effectiveness and recurrence of symptoms was not done.

**Conclusion**

To the best of our knowledge, this is the first real-world study on norethisterone 10 mg CR formulation in Indian women with AUB. AUB is the common diagnosis among cases of heavy menstrual bleeding and accounts for a significant proportion of referrals to gynecologists. Our findings suggest that norethisterone 10 mg CR formulation with the convenience of once-daily administration, short duration of treatment, and safe and effective treatment profile can be a reliable alternative to other medical and surgical treatments of AUB among women of reproductive age.

**Acknowledgment**

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**References**


