Section: Anesthesia

Systematic Review

ORMELOXIFENE VERSUS NORETHISTERONE IN THE MEDICAL MANAGEMENT OF ABNORMAL UTERINE BLEEDING: A SYSTEMATIC REVIEW

K.Karpagavalli[1], M.Sulochana Shivani[2], P.Mithun Anand[3]

[1]Assistant Professor, Department of Obstetrics and Gynaecology, CSI Medical College and Hospital, Neyyoor, Kanyakumari, Tamilnadu, India
[2]Assistant Professor, Department of Anaesthesia, Kanyakumari Medical Mission Research Centre, Kadiapattinam, Kanyakumari, Tamilnadu, India
[3]Assistant Professor, Department of ENT, Kanyakumari Medical Mission Research Centre, Kadiapattinam, Kanyakumari, Tamilnadu, India

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Corresponding Author:
Dr. K. Karpagavalli,
Email: drkkv1964@gmail.com

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ABSTRACT

Background: Abnormal uterine bleeding (AUB) is a common gynecological condition that can cause excessive menstrual blood loss, anaemia, and impaired quality of life. Ormeloxifene and norethisterone are commonly used medical treatments, but comparative evidence remains heterogeneous. The aim is to systematically review the efficacy and safety of ormeloxifene compared with norethisterone for the medical management of AUB. **Materials and Methods:** A systematic review was conducted according to the PRISMA 2020 guidelines. PubMed/MEDLINE, PubMed Central, Google Scholar, and DOAJ were searched from database inception to 24 July 2026. Comparative studies evaluating ormeloxifene versus norethisterone in women with AUB were eligible. Primary outcomes were menstrual blood loss, haemoglobin concentration, and endometrial thickness. Secondary outcomes included adverse events, patient-reported outcomes, treatment compliance, treatment discontinuation, and surgical intervention. Risk of bias was assessed using RoB 2 and ROBINS-I. **Result:** Twenty-one comparative studies involving 2,184 participants were included, with 2,102 contributing to the direct ormeloxifene-versus-norethisterone comparison. Sixteen studies were randomized controlled trials and five were non-randomized comparative or prospective cohort studies. Across studies, ormeloxifene generally produced greater reductions in menstrual blood loss, greater increases in haemoglobin, and greater reductions in endometrial thickness than norethisterone. Patient-reported symptom improvement, treatment acceptability, and compliance also generally favoured ormeloxifene. Both treatments were generally well tolerated, although menstrual disturbances were more commonly reported with ormeloxifene, while breakthrough bleeding and spotting were more frequent with norethisterone. All randomized studies had some concerns regarding risk of bias, while all non-randomized studies had serious overall risk of bias. **Conclusion:** Ormeloxifene appears to be more effective than norethisterone for reducing menstrual blood loss and endometrial thickness and improving haemoglobin levels, with better reported compliance and a broadly comparable safety profile.

INTRODUCTION

Abnormal uterine bleeding (AUB) is one of the most common reasons women seek gynecological care, affecting approximately 3%–30% of women during their reproductive years, with a higher prevalence around menarche and perimenopause.[1] Beyond being a common gynecological complaint, heavy or irregular menstrual bleeding can lead to anaemia, interfere with daily activities, and negatively affect emotional well-being and productivity.[2] Recent global estimates also show that gynecological conditions associated with abnormal bleeding, including uterine fibroids and related disorders, continue to affect a large number of women of reproductive age, with the overall burden increasing over the past three decades.[3,4] In India, AUB affects nearly 18% of women, highlighting its importance as a major public health concern rather than simply an individual clinical problem.[2]

Medical management is usually the first treatment option before surgery is considered, and norethisterone and ormeloxifene are among the most commonly used medications. Norethisterone, a

synthetic progestin, has long been used to control heavy menstrual bleeding and continues to be recommended as a first-line hormonal therapy in major evidence-based guidelines.[5] It acts by stabilizing the endometrial lining but requires daily administration, which may affect treatment adherence.[6] Ormeloxifene, is a non-steroidal selective estrogen receptor modulator (SERM) that has tissue-specific actions. It exerts anti-estrogenic effects on the uterus while preserving beneficial effects on bone and cardiovascular tissues. Its once- or twice-weekly dosing schedule has made it an attractive alternative, particularly in resource-limited settings.[2,7]

Over the past few years, several comparative studies have evaluated ormeloxifene and norethisterone using outcomes such as the Pictorial Blood Loss Assessment Chart (PBAC) score, hemoglobin concentration, and endometrial thickness.[7-9] Most studies have reported greater reductions in menstrual blood loss and better improvement in hemoglobin levels with ormeloxifene, along with a favourable safety profile and better treatment compliance.[7,9] However, these studies differ in their design, sample size, treatment protocols, and follow-up duration, making it difficult to draw consistent and widely applicable conclusions from individual studies.[10] Previous reviews on the medical management of heavy menstrual bleeding have also highlighted the limited availability of high-quality comparative evidence for newer treatment options such as ormeloxifene and have emphasized the unequal access to effective medical therapies in resource-limited settings.[5,11,12]

Given these variations in the available evidence, a comprehensive systematic review comparing ormeloxifene and norethisterone is needed. This review aims to synthesize and critically evaluate the available evidence on their efficacy, safety, and patient-reported outcomes to support evidence-based decision-making in the medical management of AUB.

Aim & objectives

Aim: To systematically review the efficacy and safety of ormeloxifene compared with norethisterone for the medical management of AUB.

Objectives

Primary Objectives

- To compare the effects of ormeloxifene and norethisterone on menstrual blood loss (PBAC or equivalent measures).
- To compare changes in hemoglobin concentration.
- To compare changes in endometrial thickness.

Secondary Objectives

- To compare the safety profiles based on reported adverse events.
- To compare patient-reported outcomes, including symptom improvement, treatment satisfaction, and compliance.
- To compare the need for treatment discontinuation or surgical intervention, where reported.

MATERIALS AND METHODS

Study Design and Reporting Guidelines: This systematic review was conducted to evaluate the efficacy and safety of ormeloxifene compared with norethisterone in the medical management of AUB. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[13] Due to the clinical and methodological heterogeneity among the included studies with respect to study design, patient characteristics, outcome assessment, and follow-up duration, a narrative synthesis was performed instead of a formal meta-analysis.

Research Question and PECO Framework: The review question was formulated using the PICO (Population, Intervention, Comparator, and Outcome) framework.

Population (P): Women of reproductive or perimenopausal age diagnosed with AUB.

Intervention (I): Treatment with ormeloxifene.

Comparator (C): Treatment with norethisterone.

Outcomes (O): The primary outcomes were changes in menstrual blood loss assessed using the PBAC or equivalent validated measures, haemoglobin concentration, and endometrial thickness. Secondary outcomes included treatment-related adverse events, patient-reported outcomes (symptom improvement, treatment satisfaction, and compliance), treatment discontinuation or surgical intervention, and methodological quality of included studies.

Protocol Registration: This systematic review was not prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) or any other systematic review registry.

Eligibility Criteria: Original comparative studies evaluating ormeloxifene and norethisterone in women with AUB were eligible for inclusion. Randomized controlled trials, prospective comparative studies, and prospective cohort studies reporting at least one outcome of interest were included irrespective of sample size or follow-up duration.

Studies were excluded if they were systematic reviews, meta-analyses, review articles, editorials, letters, conference abstracts without sufficient original data, case reports, case series, animal studies, in vitro studies, or did not directly compare ormeloxifene with norethisterone. Studies published in languages other than English were also excluded.

Information Sources and Search Strategy: A comprehensive literature search was conducted using freely accessible electronic databases, including PubMed/MEDLINE, PubMed Central (PMC), Google Scholar, and the Directory of Open Access

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Journals (DOAJ), from database inception to 24 July 2026. The electronic search was supplemented by manual screening of the reference lists of eligible studies and relevant systematic reviews to identify additional potentially eligible studies.

The search strategy combined Medical Subject Headings (MeSH), where applicable, and free-text keywords related to AUB, dysfunctional uterine bleeding, heavy menstrual bleeding, ormeloxifene, centchroman, and norethisterone. Boolean operators (AND, OR) were used to combine search terms, and the strategy was adapted for each database.

A representative search strategy was: ("abnormal uterine bleeding" OR "heavy menstrual bleeding" OR "dysfunctional uterine bleeding") AND ("ormeloxifene" OR "centchroman") AND ("norethisterone" OR "norethisterone acetate").

No restrictions on publication year were applied. Only studies published in English were considered eligible.

Study Selection: Records retrieved from the electronic databases were organized and screened manually using Microsoft Excel. Duplicate records were removed before screening. Titles and abstracts were assessed according to the predefined eligibility criteria, followed by full-text evaluation of potentially eligible studies. Study selection was performed by a single reviewer. The overall study selection process was documented using a PRISMA 2020 flow diagram.

Data Extraction: Data were extracted by a single reviewer using a standardized data extraction form. Extracted information included author, publication year, country, study design, study classification, sample size, study population, intervention and comparator details, duration of follow-up, and reported outcomes.

Outcome data included menstrual blood loss (PBAC score or equivalent validated measures), hemoglobin concentration, endometrial thickness, adverse events, patient-reported outcomes, treatment discontinuation, surgical intervention, and overall study findings. Where outcome data were unavailable or incompletely reported, they were recorded as "not reported" without further assumptions.

Outcomes of Interest: The primary outcomes were changes in menstrual blood loss, hemoglobin concentration, and endometrial thickness following treatment with ormeloxifene or norethisterone.

Secondary outcomes included treatment-related adverse events, patient-reported outcomes such as symptom improvement, treatment satisfaction, and compliance, treatment discontinuation, surgical intervention including hysterectomy where reported, and the methodological quality of the included studies.

Risk of Bias Assessment: The methodological quality of the included studies was assessed according to study design. Randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool.[14] Whereas non-randomized studies were assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool.[15] The results of the risk-of-bias assessment were summarized using traffic-light plots and summary plots generated with the ROBVIS visualization tool.[16]

Data Synthesis: A quantitative meta-analysis was not performed because of substantial clinical and methodological heterogeneity among the included studies, including variations in study design, sample size, outcome assessment methods, and follow-up duration. Therefore, findings were synthesized narratively.

Study characteristics were summarized descriptively. Primary efficacy outcomes, including menstrual blood loss, hemoglobin concentration, and endometrial thickness, were synthesized across studies. Secondary outcomes, including adverse events, patient-reported outcomes, treatment discontinuation, and surgical intervention, were also summarized descriptively. Risk-of-bias findings for randomized and non-randomized studies were presented separately using the RoB 2 and ROBINS-I assessment tools.

RESULTS

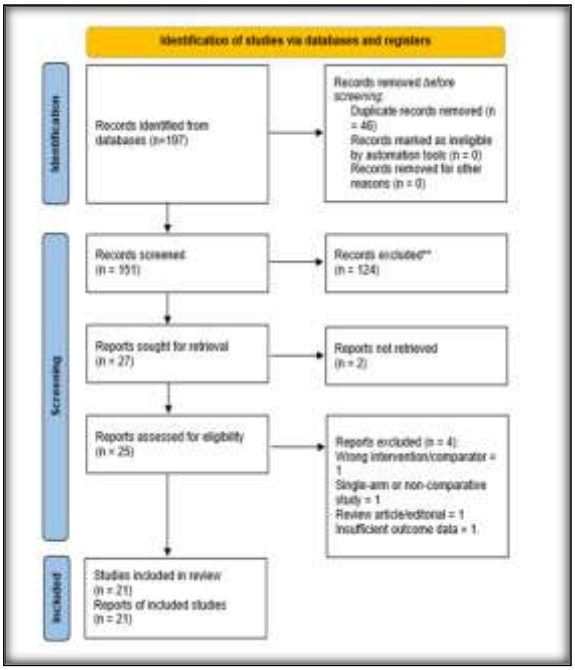

Figure 1: PRISMA 2020 Flow Diagram

Study Selection and Characteristics: Twenty-one comparative studies published between 2013 and 2026 met the eligibility criteria, comprising a total of 2,184 participants enrolled or reported across the included studies. Of these, 2,102 participants contributed to the direct ormeloxifene-versus-norethisterone comparison, after excluding the 75 participants assigned to the conventional oral contraceptive pill arm in the three-arm study and seven participants who were enrolled but not included in the final analysis of one study. The characteristics of the included studies are

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summarized in Table 1. Sample sizes ranged from 30 to 300 participants. Sixteen studies were classified as randomized controlled trials, while five were classified as non-randomized comparative or prospective cohort studies. Follow-up duration ranged from 3 to 6 months, with one study including an additional 3-month post-treatment follow-up after 6 months of therapy. All studies were conducted in India and directly compared oral ormeloxifene with oral norethisterone, although dosing schedules and treatment durations varied. One three-arm study also included a conventional oral contraceptive pill arm, which was excluded from the present synthesis because it was outside the predefined comparison.[8,17-36]

Table 1: Characteristics of included studies

Study	Year	Country	Study Design	Design Classification	Sample Size (n)	Population	Intervention	Comparator	Follow-up	Outcomes Assessed
Agarwal et al,[17]	2013	India	Prospective comparative study	RCT	100 (50/50)	Women with AUB	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	6 months	PBAC, Hb, ET, subjective improvement, adverse events
Chitrangada et al,[18]	2014	India	Double-blinded randomized controlled trial	RCT	100 (50/50)	Women with menorrhagia (18–51 years)	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	6 months	PBAC, Hb, ET, subjective improvement, adverse events
Jacob et al,[19]	2015	India	Comparative study	RCT	30 (15/15)	Perimenopausal women with AUB	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	3 months	PBAC, Hb, ET
Cardoso et al,[20]	2016	India	Prospective randomized study	RCT	63 (33/30)	Perimenopausal women with AUB	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	6 months	PBAC, Hb, ET, subjective improvement, adverse events
Karmakar & Deshpande,[21]	2016	India	Randomized study	RCT	100 (50/50)	Women with AUB (30–50 years, completed childbearing)	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	6 months + 3-month post-treatment follow-up	PBAC, Hb, ET, adverse events
Talukdar et al,[22]	2016	India	Prospective, comparative, interventional randomized study	RCT	60 (30/30)	Women with AUB, early reproductive age	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	6 months	PBAC, Hb, ET, adverse events, dysmenorrhea, hysterectomy
Chauhan et al,[23]	2017	India	Randomized study (three-arm)	RCT	300 (111/114 ORM/NET; 75 OCP)	Women with AUB	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	6 months	Subjective improvement, Hb, ET
Amruta & Pawaskar,[24]	2018	India	Comparative study	Non-RCT	100 (50/50)	Women with DUB (40–55 years)	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	6 months	PBAC, Hb, ET, adverse events, hysterectomy
Gett & Singh,[25]	2018	India	Prospective comparative study	Non-RCT	100 (50/50)	Women with DUB (20–50 years)	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	3 months	PBAC, Hb, ET, adverse events, cost

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Agrawal et al.[26]	2019	India	Prospective randomized comparative study	RCT	100 (50/50)	Perimenopausal women with DUB (40–55 years)	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	6 months	PBAC, Hb, ET, adverse events, hysterectomy
Surabhi & Chandra, [8]	2019	India	Prospective randomized comparative study	RCT	60 (30/30)	Perimenopausal women with DUB (40–50 years)	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	6 months	PBAC, Hb, ET
Vardaini et al.[27]	2020	India	Prospective randomized comparative study	RCT	100 (50/50)	Women with AUB-O (25–45 years)	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	3 months	Hb, ET
Meena et al.[28]	2022	India	Prospective comparative study	RCT	300 (150/150)	Perimenopausal women with AUB (35–52 years)	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	6 months	Menstrual blood loss (pads/clots), Hb, adverse events
Srinivasan et al.[29]	2022	India	Prospective randomized double-blinded study	RCT	61 (30/31)	Women with AUB (19–45 years)	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	3 months	Hb, ET
Das et al.[30]	2023	India	Prospective comparative study	Non-RCT	100 (50/50)	Perimenopausal women with DUB (40–55 years)	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	3 months	PBAC, Hb, ET, adverse events, cost
Fatima & Siddiqua, [31]	2024	India	Prospective comparative study	Non-RCT	100 (50/50)	Women with heavy menstrual bleeding (30–50 years)	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	6 months	PBAC, Hb, ET, subjective improvement, adverse events
Jadaun et al.[32]	2024	India	Randomized comparative study	RCT	70 enrolled; 63 analyzed (31/32)	Women with AUB (25–40 years)	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	6 months	PBAC, Hb, ET, adverse events
Gawande et al.[33]	2025	India	Randomized controlled trial	RCT	60 (30/30)	Women with AUB (21–47 years)	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	6 months	PBAC, Hb, ET, adverse events, hysterectomy rate
Mainani et al.[34]	2025	India	Prospective comparative clinical study	RCT	100 (50/50)	Women ≥35 years with AUB	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	4 months	PBAC, Hb, ET, adverse events
Shanmuga Sundhari et al.[35]	2025	India	Randomized comparative study	RCT	120 (60/60)	Women with AUB, predominantly 40–49 years	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	6 months	Modified menstrual blood-loss scale, Hb, serum ferritin, adverse events, dysmenorrhea
Singh, Kundu & Kundu.[36]	2026	India	Prospective cohort study	Non-RCT	60 (30/30)	Women with heavy menstrual bleeding	Ormeloxifene 60 mg oral regimen	Norethisterone 5 mg oral regimen	6 months	PBAC, Hb (qualitative only), ET,

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						(30–40 years)				amenorrhea

RCT: randomized controlled trial; PBAC: Pictorial Blood Loss Assessment Chart; Hb: hemoglobin; ET: endometrial thickness.

Menstrual Blood Loss: Menstrual blood loss was assessed using the PBAC or other quantitative or modified scoring measures in several studies, while Meena et al. assessed bleeding using daily sanitary pad and clot frequency rather than a formal PBAC score.28 The primary efficacy findings are summarized in [Table 2]. In the largest study, Meena et al. (n=300), daily pad usage decreased from 9.86 to 1.45 with ormeloxifene and from 10.80 to 3.13 with norethisterone at 6 months; clot frequency also decreased from 2.62 to 0.04 and from 2.47 to 0.55, respectively.28 Agarwal et al. reported a reduction in PBAC score from 216 to 84 with ormeloxifene compared with 232 to 170 with norethisterone.17 Chitrangada et al. similarly reported reductions from 196.46 to 79.57 and from 186.35 to 105.76, respectively.18 Cardoso et al. reported reductions from 224 to 80 with ormeloxifene and from 253 to 165 with norethisterone.[20]

Talukdar et al. reported PBAC reductions from 176.80 to 29.13 with ormeloxifene and from 179.73 to 86.87 with norethisterone (p=0.0035).22 Amruta and Pawaskar reported reductions from 225 to 75 and from 234 to 110, respectively (p<0.01).24 Gett and Singh reported reductions from 274 to 91.7 with ormeloxifene and from 274 to 188 with norethisterone, although only within-group significance was reported.25 Agrawal et al. reported reductions from 285.34 to 74.11 versus 234.56 to 108.21 (p<0.001).26 Surabhi and Chandra reported reductions from 294.33 to 64.11 with ormeloxifene and from 288.56 to 103.55 with norethisterone.[8] Das et al. reported reductions from 274 to 90 versus 273 to 190 (p<0.001).30 Fatima and Siddiqua reported reductions from 202.44 to 122.22 versus 215.86 to 162.16.31 Jadaun et al. reported reductions from 244.2 to 65.7 versus 237.5 to 85.3, although only within-group significance was reported.32 Gawande et al. reported reductions from 177.63 to 53.00 versus 178.33 to 74.60.33 Mainani et al. reported reductions from 283.54 to 67.62 versus 268.10 to 99.94.34 Shanmuga Sundhari et al. demonstrated improvement using a modified menstrual blood-loss scale, with scores decreasing from 11.18 to 7.43 with ormeloxifene and from 11.46 to 8.17 with norethisterone.[35] Singh, Kundu and Kundu reported reductions in PBAC scores from 361.80 to 69.20 with ormeloxifene and from 376.87 to 109.40 with norethisterone.[36] Overall, the reported findings consistently showed a greater numerical reduction in menstrual blood loss with ormeloxifene, although the statistical evidence for between-group differences was not uniformly reported across studies.

Table 2: Primary Efficacy Outcomes of Included Studies

Study	Menstrual Blood Loss (Baseline → Final)	Hemoglobin (g/dL) (Baseline → Final)	Endometrial Thickness (mm) (Baseline → Final)	Overall Finding
Agarwal et al.17	ORM: 216 → 84; NET: 232 → 170	ORM: 7.52 → 10.40; NET: 7.48 → 8.60	ORM: 12.12 → 8.40; NET: 12.05 → 9.80	Favoured Ormeloxifene
Chitrangada et al.18	ORM: 196.46 → 79.57; NET: 186.35 → 105.76	ORM: 7.27 → 8.99; NET: 7.42 → 8.33	ORM: 5.49 → 4.49; NET: 5.08 → 4.83	Favoured Ormeloxifene
Jacob et al.19	ORM: 277.33 → 70.11; NET: 246.00 → 108.50	ORM: 9.68 → 11.07; NET: 10.17 → 10.58	ORM: 7.80 → 5.30; NET: 6.70 → 5.90	Favoured Ormeloxifene
Cardoso et al.20	ORM: 224 → 80; NET: 253 → 165	ORM: 8.52 → 10.50; NET: 8.28 → 8.70	ORM: 12.09 → 8.20; NET: 12.07 → 10.80	Favoured Ormeloxifene
Karmakar & Deshpande21	ORM: 227.36 → 62.00; NET: 190.08 → 92.00	ORM: 8.23 → 11.67; NET: 8.32 → 10.17	ORM: 9.33 → 5.23; NET: 8.65 → 6.84	Favoured Ormeloxifene
Talukdar et al.22	ORM: 176.80 → 29.13; NET: 179.73 → 86.87 (p=0.0035)	ORM: 8.84 → 10.38; NET: 8.78 → 9.28 (p=0.0031)	ORM: 8.99 → 2.48; NET: 7.86 → 5.90 (p=0.0035)	Favoured Ormeloxifene
Chauhan et al.23	NR	Numerical values not reported; ORM superior	Numerical values not reported; ORM superior	Favoured Ormeloxifene
Amruta & Pawaskar24	ORM: 225 → 75; NET: 234 → 110 (p<0.01)	ORM: 7.2 → 10.5; NET: 7.6 → 9.9 (p<0.05)	ORM: 11.8 → 6.6; NET: 11.2 → 8.1 (p<0.05)	Favoured Ormeloxifene
Gett & Singh25	ORM: 274 → 91.7; NET: 274 → 188 (within-group p only)	ORM: 7.3 → 9.6; NET: 7.5 → 8.5	ORM: 11.9 → 7.9; NET: 11.7 → 10.3	Favoured ormeloxifene; between-group significance not reported

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Agrawal et al.26	ORM: 285.34 → 74.11; NET: 234.56 → 108.21 (p<0.001)	ORM: 9.1 → 11.4; NET: 9.2 → 10.5 (p<0.001)	ORM: 7.4 → 5.4; NET: 6.9 → 5.7 (p<0.001)	Favoured Ormeloxifene
Surabhi & Chandra8	ORM: 294.33 → 64.11; NET: 288.56 → 103.55	ORM: 9.02 → 11.51; NET: 9.12 → 10.43	ORM: 7.4 → 5.1 (within-group p<0.001); NET: 6.9 → 5.7 (within-group p=0.109, NS)	Favoured Ormeloxifene
Vardaini et al.27	NR	ORM: 8.85 → 11.68; NET: 8.75 → 10.54	ORM: 11.94 → 8.08; NET: 11.83 → 9.56	Favoured Ormeloxifene
Meena et al.28	Pads/day: ORM: 9.86 → 1.45; NET: 10.80 → 3.13; Clots: ORM: 2.62 → 0.04; NET: 2.47 → 0.55	ORM: 9.99 → 11.75; NET: 9.89 → 11.00	NR	Favoured ormeloxifene overall; between-group hemoglobin difference not significant
Srinivasan et al.29	NR	ORM: 8.30 → 10.30; NET: 9.00 → 10.40	ORM: 9.30 → 7.80; NET: 8.30 → 7.20	Favoured Ormeloxifene
Das et al.30	ORM: 274 → 90; NET: 273 → 190 (p<0.001)	ORM: 7.57 → 9.8; NET: 6.92 → 8.2 (p<0.001)	ORM: 11.81 → 7.6; NET: 11.86 → 10.5 (p<0.001)	Favoured Ormeloxifene
Fatima & Siddiqua31	ORM: 202.44 → 122.22; NET: 215.86 → 162.16	ORM: 8.50 → 9.20; NET: 8.35 → 8.63	ORM: 11.08 → 7.60; NET: 10.81 → 9.05	Favoured Ormeloxifene
Jadaun et al.32	ORM: 244.2 → 65.7; NET: 237.5 → 85.3 (within-group p<0.0001 only)	ORM: 8.1 → 10.2; NET: 8.2 → 9.6	ORM: 8.9 → 6.1; NET: 9.1 → 7.2	Favoured ormeloxifene; between-group significance not reported
Gawande et al.33	ORM: 177.63 → 53.00; NET: 178.33 → 74.60	ORM: 9.04 → 11.31; NET: 9.31 → 11.22	ORM: 12.11 → 3.21; NET: 12.12 → 5.92	Favoured Ormeloxifene
Mainani et al.34	ORM: 283.54 → 67.62; NET: 268.10 → 99.94	ORM: 9.12 → 12.03; NET: 9.17 → 10.48	ORM: 8.89 → 4.80; NET: 9.16 → 5.66	Favoured Ormeloxifene
Shanmuga Sundhari et al.35	ORM: 11.18 → 7.43; NET: 11.46 → 8.17 (modified scale)	ORM: 8.98 → 11.9; NET: 9.01 → 11.1 (p=0.008)	NR	Favoured Ormeloxifene
Singh, Kundu & Kundu36	ORM: 361.80 → 69.20; NET: 376.87 → 109.40	NR; qualitative improvement reported	ORM: 11.47 → 6.73; NET: 11.08 → 8.59	Favoured ormeloxifene

ORM: ormeloxifene; NET: norethisterone; PBAC: Pictorial Blood Loss Assessment Chart; Hb: hemoglobin; ET: endometrial thickness; NR: not reported.

Hemoglobin Concentration: Hemoglobin concentration increased from baseline in both treatment groups, with greater numerical improvement generally observed with ormeloxifene. Talukdar et al. reported increases from 8.84 to 10.38 g/dL with ormeloxifene versus 8.78 to 9.28 g/dL with norethisterone (p=0.0031).22 Amruta and Pawaskar reported increases from 7.2 to 10.5 g/dL versus 7.6 to 9.9 g/dL (p<0.05), while Gett and Singh reported increases from 7.3 to 9.6 g/dL versus 7.5 to 8.5 g/dL, with only within-group significance reported.24,25 Agrawal et al. reported increases from 9.1 to 11.4 g/dL versus 9.2 to 10.5 g/dL (p<0.001).[26]

Studies similarly showed greater numerical increases with ormeloxifene, including Agarwal et al. (7.52→10.40 vs 7.48→8.60 g/dL), Chitrangada et al. (7.27→8.99 vs 7.42→8.33 g/dL), Cardoso et al. (8.52→10.50 vs 8.28→8.70 g/dL), Karmakar and Deshpande (8.23→11.67 vs 8.32→10.17 g/dL), and Surabhi and Chandra (9.02→11.51 vs 9.12→10.43 g/dL).8,17,18,20,21 More recent studies also demonstrated similar trends: Meena et al. (9.99→11.75 vs 9.89→11.00 g/dL), Srinivasan et al. (8.30→10.30 vs 9.00→10.40 g/dL), Das et al. (7.57→9.8 vs 6.92→8.2 g/dL; p<0.001), Fatima and Siddiqua (8.50→9.20 vs 8.35→8.63 g/dL), Jadaun et al. (8.1→10.2 vs 8.2→9.6 g/dL), Gawande et al. (9.04→11.31 vs 9.31→11.22 g/dL), and Mainani et al. (9.12→12.03 vs 9.17→10.48 g/dL).28-34 Shanmuga Sundhari et al. reported increases from 8.98 to 11.9 g/dL versus 9.01 to 11.1 g/dL (p=0.008).35 Singh, Kundu and Kundu reported qualitative improvement without numerical hemoglobin values.[36] Overall, hemoglobin improvement generally favoured ormeloxifene, although between-group statistical comparisons were not consistently reported.

Endometrial Thickness: Endometrial thickness was reported in most included studies, with reductions generally favouring ormeloxifene. Talukdar et al. reported reductions from 8.99 to 2.48 mm with ormeloxifene compared with 7.86 to 5.90 mm with

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norethisterone (p=0.0035).22 Agarwal et al. reported reductions from 12.12 to 8.40 mm versus 12.05 to 9.80 mm.[17] Chitrangada et al. reported reductions from 5.49 to 4.49 mm versus 5.08 to 4.83 mm.18 Cardoso et al. reported reductions from 12.09 to 8.20 mm with ormeloxifene and from 12.07 to 10.80 mm with norethisterone.[20]

Karmakar and Deshpande reported reductions from 9.33 to 5.23 mm vs 8.65 to 6.84 mm.[21] Surabhi and Chandra reported a significant within-group reduction from 7.4 to 5.1 mm with ormeloxifene (p<0.001), whereas the reduction from 6.9 to 5.7 mm with norethisterone was not statistically significant (p=0.109).[8] Agrawal et al. reported reductions from 7.4 to 5.4 mm versus 6.9 to 5.7 mm (p<0.001).[26] Vardaini et al. reported reductions from 11.94 to 8.08 mm with ormeloxifene compared with 11.83 to 9.56 mm with norethisterone.[27] Srinivasan et al. reported reductions from 9.30 to 7.80 mm versus 8.30 to 7.20 mm.29 Das et al. reported reductions from 11.81 to 7.60 mm versus 11.86 to 10.50 mm (p<0.001).30 Fatima and Siddiqua reported reductions from 11.08 to 7.60 mm versus 10.81 to 9.05 mm.31 Jadaun et al. reported reductions from 8.9 to 6.1 mm versus 9.1 to 7.2 mm.32 Gawande et al. reported reductions from 12.11 to 3.21 mm versus 12.12 to 5.92 mm.33 Mainani et al. reported reductions from 8.89 to 4.80 mm versus 9.16 to 5.66 mm.34 Singh, Kundu and Kundu reported reductions from 11.47 to 6.73 mm with ormeloxifene and from 11.08 to 8.59 mm with norethisterone.36 Endometrial thickness was not reported in Chauhan et al., Meena et al., or Shanmuga Sundhari et al.[23,28,35] Overall, the reported reductions in endometrial thickness were generally greater with ormeloxifene, although between-group statistical comparisons were not consistently reported.

Safety Profile: Adverse events were generally mild or non-serious in the studies that reported safety outcomes, and the findings are summarized in [Table 3]. Ormeloxifene was most commonly associated with menstrual disturbances, including amenorrhea, hypomenorrhea, and oligomenorrhea. Chitrangada et al. reported amenorrhea in 8%, hypomenorrhea in 10%, and ovarian cysts in 12% of women receiving ormeloxifene.[18] Karmakar and Deshpande reported amenorrhea in 28%, hypomenorrhea in 12%, spotting in 4%, and uterovaginal prolapse in 2%.21 Other studies reported oligomenorrhea, headache, nausea, breast tenderness, and delayed menstruation with ormeloxifene.[28,31,34]

Norethisterone was associated with breakthrough bleeding, spotting, nausea, abdominal symptoms, acne, and other minor adverse effects.[17,18,28,34] In study by Gett and Singh, the difference in mild adverse events between treatment groups was not statistically significant.25 Similarly, Gawande et al. reported adverse events in 23.3% of women receiving ormeloxifene and 6.7% receiving norethisterone, with no statistically significant between-group difference (p=0.148).33 Overall, the reported adverse events were predominantly mild, although the type and frequency of adverse events varied across studies.

Table 3: Adverse Events, Patient-Reported Outcomes, and Surgical Intervention of Included Studies

Study	Adverse Events – Ormeloxifene	Adverse Events – Norethisterone	Subjective Improvement / Patient Satisfaction	Surgical Intervention / Treatment Discontinuation
Agarwal et al.17	Amenorrhea (8%), hypomenorrhea (8%), nausea/vomiting/headache (4%)	Breakthrough bleeding (4%), spotting (14%)	Marked improvement: 88% vs 74%	NR
Chitrangada et al.18	Nausea (20%), abdominal pain (16%), ovarian cyst (12%), white discharge/cervical symptoms (14%), amenorrhea (8%), hypomenorrhea (10%), headache (2%)	Nausea (24%), abdominal pain (16%), white discharge/cervical symptoms (10%), hypomenorrhea (4%), breakthrough bleeding (14%), spotting (8%), headache (4%)	Better subjective improvement with ORM	NR
Jacob et al.19	Amenorrhea (20%); no major adverse events	No major adverse events	Formal assessment not reported	Some patients required surgery because of treatment failure; numbers not specified
Cardoso et al.20	No major adverse events; one hysterectomy	Four patients discontinued because of bloating and mastalgia	Marked improvement: 81% vs 66%	One hysterectomy (ORM); four discontinuations (NET)
Karmakar & Deshpande21	Amenorrhea (28%), hypomenorrhea (12%), spotting (4%), uterovaginal prolapse (2%)	Hypomenorrhea (2%), spotting (12%), breakthrough bleeding (2%)	Better acceptability with ORM	No surgery; participants who withdrew were replaced
Talukdar et al.22	Amenorrhea (13%)	No amenorrhea reported	Satisfaction: 80% vs 56% (p=0.0946); difference not statistically significant	Hysterectomy: 20% vs 44%
Chauhan et al.23	NR	NR	Better improvement in general health, vaginal bleeding, abdominal pain,	NR

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			social and sexual activity with ORM	
Amruta & Pawaska24	No major adverse events reported	No major adverse events reported	Better symptom control with ORM	Hysterectomy: 23% vs 45%
Gett & Singh25	Mild adverse events reported; between-group difference not significant	Mild adverse events reported; between-group difference not significant	Better acceptability/compliance with ORM; cost advantage reported	NR
Agrawal et al.26	Amenorrhea was the main reported adverse event	Adverse events reported; details as reported in the study	Better clinical response with ORM	Surgical management/hysterectomy: 20% vs 42%
Surabhi & Chandra8	No major adverse events reported	No major adverse events reported	Better compliance and tolerability with ORM	NR
Vardaini et al.27	No major adverse events	No major adverse events	Better compliance and cost-effectiveness with ORM	NR
Meena et al.28	Weight gain (0.67%), delayed menstruation (0.67%)	Abdominal pain, nausea, vomiting, dizziness, breast tenderness, weight gain	Better compliance with ORM	NR
Srinivasan et al.29	No major adverse events	No major adverse events	Better compliance with ORM	NR
Das et al.30	Mild adverse events reported	Mild adverse events reported	Better acceptability/compliance with ORM; cost advantage reported	NR
Fatima & Siddiqua31	Oligomenorrhea (8%), nausea (2%), weight gain (2%), headache (2%)	Nausea (18%), weight gain (10%), headache (4%), oligomenorrhea (2%)	Marked improvement: 76% vs 38%	NR
Jadaun et al.32	Amenorrhea (54.8%) reported	No amenorrhea reported	Better symptom improvement/response with ORM	NR
Gawande et al.33	Amenorrhea, headache, nausea; mild adverse events	Mild adverse events in two patients	Formal assessment not reported; outcomes favoured ORM	Hysterectomy: 1 vs 2
Mainani et al.34	Breast tenderness (12%)	Acne (10%), gastrointestinal symptoms (6%), breast tenderness (8%)	Better compliance with ORM	NR
Shanmuga Sundhari et al.35	Amenorrhea (10%); menstrual clots and dysmenorrhea improved	Menstrual clots and dysmenorrhea improved	Better symptom improvement with ORM	NR
Singh, Kundu & Kundu36	Amenorrhea (3.3%); no major adverse events	Amenorrhea (6.7%); no major adverse events	Better compliance and symptom relief with ORM	NR

ORM: ormeloxifene; NET: norethisterone; NR: Not reported.

Patient-Reported Outcomes: Subjective improvement, treatment satisfaction, and treatment compliance generally favoured ormeloxifene. Subjective improvement was reported in 88% versus 74% of participants,[17] and 81% versus 66% in another study.20 A more recent comparative study reported subjective improvement in 76% versus 38% of participants.[31] Greater improvement in general health, vaginal bleeding, abdominal pain, social activity, and sexual activity was also reported with ormeloxifene.[23] Higher treatment acceptability or compliance was reported across several studies.[2,21,24,25,27,29,34,36] In one study, treatment satisfaction was higher with ormeloxifene than norethisterone (80% vs 56%), although the difference was not statistically significant (p=0.0946).[22] Overall, patient-reported outcomes generally favoured ormeloxifene, although assessment methods varied across studies.

Treatment Discontinuation and Surgical Intervention: Treatment discontinuation and surgical outcomes were reported inconsistently across the included studies. Four participants receiving norethisterone discontinued treatment because of bloating and mastalgia, while one participant receiving ormeloxifene underwent hysterectomy.[20] Hysterectomy was reported in 20% versus 44% of participants in one study,[22] 23% versus 45% in another,[24] and 20% vs 42% for surgical management/hysterectomy in another.26 Gawande et al. reported hysterectomy in 1 participant receiving ormeloxifene and 2 receiving norethisterone.[33] Another study reported that some participants required surgery because of treatment failure, although the numbers were not specified.[19] Most of the remaining studies did not report treatment discontinuation or surgical intervention.

Risk of Bias Assessment: Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool for

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the 16 randomized controlled trials and the ROBINS-I tool for the five non-randomized studies.[14–16] Among the randomized trials, all 16 studies were judged to have some concerns regarding overall risk of bias, with none classified as having low or high overall risk. Concerns were mainly related to the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported results. The non-randomized studies were assessed using ROBINS-I, and all five studies were judged to have a serious overall risk of bias, with the main concerns related to confounding, deviations from intended interventions, measurement of outcomes, and selection of the reported results. Detailed domain-level and overall risk-of-bias assessments are presented in [Figures 2–5].

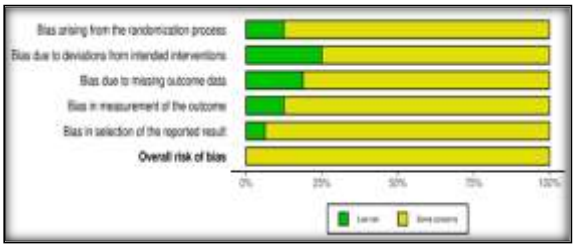

Figure 2: Summary risk-of-bias assessment of randomized controlled trials using the Cochrane RoB 2 tool.

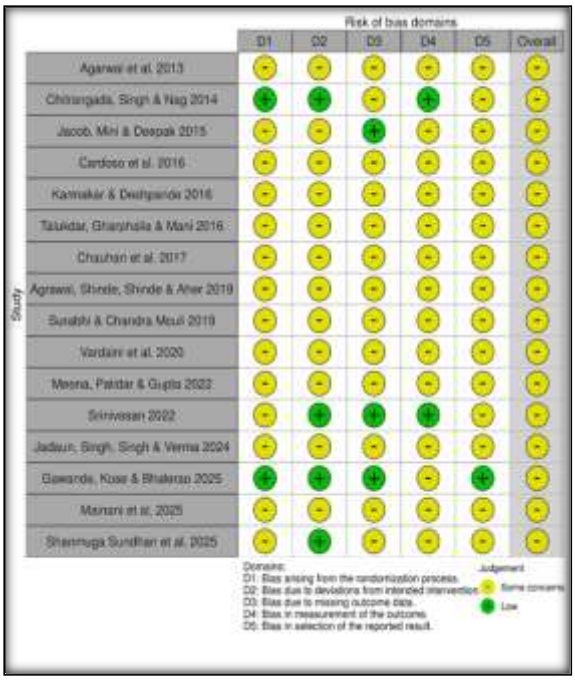

Figure 3: Traffic-light plot of risk-of-bias assessment for randomized controlled trials using the Cochrane RoB 2 tool.

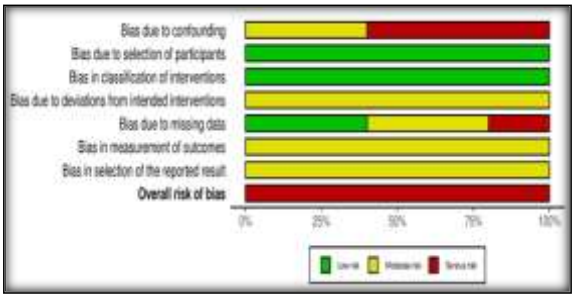

Figure 4: Summary risk-of-bias assessment of non-randomized studies using the ROBINS-I tool.

Among the 16 RCTs, all were judged to have some concerns overall, with concerns most frequently related to the randomization process and selection of the reported result. Additional concerns were identified for deviations from intended interventions, missing outcome data, and outcome measurement. All five non-randomized studies were judged to have serious overall risk of bias, primarily because of confounding and additional concerns related to deviations from intended interventions, outcome measurement, and selection of reported results.

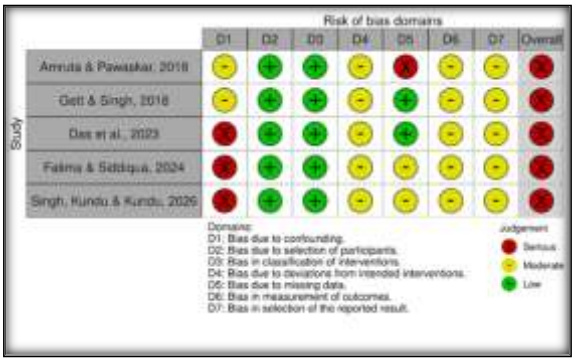

Figure 5: Traffic-light plot of risk-of-bias assessment for non-randomized studies using the ROBINS-I tool.

DISCUSSION

The purpose of this systematic review was to investigate the efficacy and safety of ormeloxifene and norethisterone in treating patients with AUB. Altogether, 21 comparative studies involving 2,184 participants enrolled or reported across the included studies were evaluated, with 2,102 participants contributing to the direct ormeloxifene-versus-norethisterone comparison. In general, the available evidence demonstrated that ormeloxifene produced better results in terms of blood loss reduction, endometrial thinning, improvement in hemoglobin levels, and treatment adherence compared with norethisterone.

Findings associated with menstrual blood loss were mostly consistent across the reviewed studies. Despite variation in the measurement of bleeding, including PBAC as well as other tools such as pad or clot counting and modified bleeding scales, the reported findings generally favoured ormeloxifene over norethisterone.[8,17-26,30-36] Although the

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magnitude of improvement varied, the overall direction of effect remained similar. Variability in treatment effects may be related to differences in baseline disease severity, treatment duration, dosing schedules, and methods used to assess menstrual blood loss rather than differences in the overall efficacy of the drugs. Such variation is also consistent with the heterogeneity reported in previous systematic reviews and meta-analyses.[7,9]

Hemoglobin levels also improved in both treatment groups, with most studies showing greater numerical improvement with ormeloxifene.[8,17-22,24--36] This finding is biologically plausible because better control of menstrual blood loss would be expected to improve hemoglobin levels over time.[28,37] Between-group statistical significance was not consistently reported, and some studies showed only numerical differences favouring ormeloxifene.[25-32] Overall, the findings suggest a favourable effect of ormeloxifene on hemoglobin recovery, although the strength of evidence varied across studies.

A similar pattern was observed for endometrial thickness. Most studies demonstrated greater reductions with ormeloxifene than with norethisterone.[8,17-22,24,26,27,34,36] This finding is consistent with the pharmacological action of ormeloxifene as a selective estrogen receptor modulator that produces anti-estrogenic effects on the endometrium, whereas norethisterone primarily acts by stabilizing the endometrial lining through its progestogenic activity.[6,37] Endometrial thickness was not reported in some studies, and one study assessed menstrual blood loss using pad and clot counts rather than PBAC.23,28,35 These differences in outcome assessment highlight the lack of uniformity across studies and make direct comparison of results more difficult.

Both medications were generally well tolerated, although the pattern of adverse events differed between treatment groups. Ormeloxifene was more commonly associated with amenorrhea, hypomenorrhea, oligomenorrhea, and occasional ovarian cysts, whereas norethisterone was more frequently associated with breakthrough bleeding, spotting, and gastrointestinal symptoms.[17,18,21,28,31,34] Amenorrhea associated with ormeloxifene was often reported as an acceptable outcome, particularly among women who had completed childbearing, rather than as a reason for treatment discontinuation.[21,22,24] Treatment compliance and acceptability were also better with ormeloxifene, related in part to its once- or twice-weekly dosing schedule compared with the daily dosing required for norethisterone.[8,21,24,25,28,29,34,36] This observation is also consistent with broader evidence suggesting that less frequent dosing can improve medication adherence.[38]

Although the overall findings favoured ormeloxifene, several limitations should be considered when interpreting the results. The included studies differed in design, sample size, follow-up duration, and methods used to measure treatment outcomes. Although most studies were randomized trials, several had concerns regarding risk of bias, particularly because of inadequate reporting of the randomization process. Outcome reporting was also inconsistent, with several studies not reporting all primary outcomes and some using non-standardized measures of menstrual blood loss instead of PBAC.[26,28,35] All included studies were conducted in India, which may limit the generalizability of the findings to other populations and healthcare settings. Because of the clinical and methodological heterogeneity among studies, a meta-analysis was not considered appropriate, and the evidence was therefore synthesized narratively. Furthermore, study selection, data extraction, and risk-of-bias assessment were performed by a single reviewer, which may have increased the possibility of selection and extraction bias despite the use of predefined eligibility criteria and a standardized data extraction form.

Future research should focus on well-designed, adequately powered, multicenter randomized controlled trials with standardized outcome measures and longer follow-up periods to better evaluate the long-term efficacy and safety of both treatments. Although previous systematic reviews have generally supported the effectiveness of ormeloxifene, additional high-quality comparative studies are needed to strengthen the available evidence. Future meta-analyses incorporating these studies may provide more precise estimates of treatment effectiveness and safety, thereby supporting stronger evidence-based recommendations for the medical management of AUB.

CONCLUSION

Ormeloxifene appears to be a more effective treatment than norethisterone for women with AUB. Across the included studies, it generally produced greater reductions in menstrual blood loss and endometrial thickness, greater improvement in haemoglobin levels, and better treatment compliance, with a broadly comparable safety profile. Larger, well-designed multicentre studies are needed to confirm these findings and strengthen the available evidence.

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