Review

Nonsurgical Management of Heavy Menstrual Bleeding

A Systematic Review

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OBJECTIVE: To compare the effectiveness of nonsurgical abnormal uterine bleeding treatments for bleeding control, quality of life (QOL), pain, sexual health, patient satisfaction, additional treatments needed, and adverse events.

DATA SOURCES: MEDLINE, Cochrane databases, and Clinicaltrials.gov were searched from inception to May 2012. We included randomized controlled trials of nonsurgical treatments for abnormal uterine bleeding presumed secondary to endometrial dysfunction and abnormal uterine bleeding presumed secondary to ovulatory dysfunction. Interventions included the levonorgestrel intrauterine system, combined oral contraceptive pills (OCPs), progestins, nonsteroidal anti-inflammatory drugs (NSAIDs), and antifibrinolytics. Gonadotropin-releasing hormone agonists, danazol, and placebo were allowed as comparators.

METHODS OF STUDY SELECTION: Two reviewers independently screened 5,848 citations and extracted eligible trials. Studies were assessed for quality and strength of evidence.

TABULATION, INTEGRATION, AND RESULTS: Twenty-six articles met inclusion criteria. For reduction of menstrual bleeding in women with abnormal uterine bleeding presumed secondary to endometrial dysfunction, the levonorgestrel intrauterine system (71–95% reduction), combined OCPs (35–69% reduction), extended cycle oral progestins (87% reduction), tranexamic acid (26–54% reduction), and NSAIDs (10–52% reduction) were all effective treatments. The levonorgestrel intrauterine system, combined OCPs, and antifibrinolytics were all superior to luteal-phase progestins (20% increase in bleeding to 67% reduction). The levonorgestrel intrauterine system was superior to combined OCPs and NSAIDs. Antifibrinolytics were superior to NSAIDs for menstrual bleeding reduction. Data were limited on other important outcomes such as QOL for women with abnormal uterine bleeding presumed secondary to endometrial dysfunction and for all outcomes for women with abnormal uterine bleeding presumed secondary to ovulatory dysfunction.

CONCLUSION: For the reduction in mean blood loss in women with heavy menstrual bleeding presumed secondary to abnormal uterine bleeding presumed secondary to endometrial dysfunction, we recommend the use of the levonorgestrel intrauterine system over OCPs, luteal-phase progestins, and NSAIDs. For other outcomes (QOL, pain, sexual health, patient satisfaction, additional treatments needed, and adverse events) and for treatment of abnormal uterine bleeding presumed secondary to ovulatory dysfunction, we were unable to make recommendations based on the limited available data.

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Women with abnormal uterine bleeding experience diminished quality of life (QOL),[1] lose

work productivity,[2] and use expensive medical resources.[2] Abnormal uterine bleeding is a symptom of several different underlying conditions, which have been newly classified by the Menstrual Disorders Working Group of the International Federation of Gynecology and Obstetrics.[3] Although hysterectomy is considered the "definitive" treatment for both abnormal uterine bleeding presumed secondary to ovulatory dysfunction and abnormal uterine bleeding presumed secondary to endometrial dysfunction, many nonsurgical options are also available and allow a woman to retain her ability to bear children and avoid a surgical intervention. Better characterization of the relative efficacy of commonly used nonsurgical therapies will allow for improved patient counseling, facilitate informed decision-making, and reduce the burden of unnecessary procedures for both the patient and the health care system.

The Systematic Review Group of the Society of Gynecologic Surgeons conducted this systematic review with the goal of producing an evidence-based guideline on nonsurgical treatment decision-making for abnormal uterine bleeding presumed secondary to ovulatory dysfunction and abnormal uterine bleeding presumed secondary to endometrial dysfunction. We specifically sought to compare the effectiveness of nonsurgical abnormal uterine bleeding treatments for bleeding control, QOL, pain, sexual health, patient satisfaction, additional treatments needed, and adverse events.

SOURCES

The Systematic Review Group of the Society of Gynecologic Surgeons, including gynecologic surgeons and systematic review methodologists, performed a systematic search to identify randomized controlled trials (RCTs) comparing treatments for abnormal uterine bleeding. A working document defining parameters for a literature search was created.[4] We searched MEDLINE and the Cochrane Central Register of Controlled Trials from inception to May 14, 2012, for English language human studies. Details of the full search were reported in a previous publication.[5] We searched www.ClinicalTrials.gov for intervention trials with results using the following terms: "abnormal uterine bleeding," "dysfunctional uterine bleeding," "menorrhagia," "menometrorrhagia," "heavy menstrual bleeding," and "uterine bleeding." Titles of studies from eligible trials were reviewed.

STUDY SELECTION

Participants of interest were defined as women receiving nonsurgical interventions for abnormal uterine bleeding secondary to presumed endometrial dysfunction or ovulatory dysfunction. Nonsurgical interventions of interest included oral synthetic progestin (luteal-phase and extended treatments), depot medroxyprogesterone acetate, combined oral contraceptive pills (OCPs), the levonorgestrel intrauterine system, nonsteroidal anti-inflammatory drugs (NSAIDs) (mefenamic acid and naproxen sodium), and antifibrinolytic treatment (tranexamic acid). Comparators of interest included all of the interventions of interest listed plus placebo. At the outset of the study, we decided to include danazol, gonadotropin-releasing hormone agonists, and ethamsylate as comparators, but not interventions, because they are not commonly used as first-line treatments for abnormal uterine bleeding.[6] Studies were excluded if they were not a RCT, if the study included a surgical comparator, or if the study included participants with abnormal uterine bleeding attributed to leiomyomata. Outcomes of interest for this review (bleeding, QOL, pain, sexual health, patient satisfaction, additional treatment, and adverse events) were defined according to a structured process, which has previously been published by the Systematic Review Group of the Society of Gynecologic Surgeons.[5]

Titles, abstracts, and full texts were screened for eligibility by two reviewers and any discrepancies were resolved by a third reviewer. Data from studies were extracted by members of the Systematic Review Group, most of whom had experience from prior systematic reviews. Individual extractions were confirmed by a second member and discrepancies were resolved by consensus. We collected data on study characteristics, participant characteristics, details on the interventions, length of follow-up, outcomes of interest measured, and how these outcomes were assessed. The classification of a study population (as abnormal uterine bleeding secondary to endometrial dysfunction, abnormal uterine bleeding secondary to ovulatory dysfunction, or mixed or uncertain) was based on description of the study population within the individual manuscripts.

We assessed the methodologic quality of each study using predefined criteria from a three-category system modified from the Agency for Healthcare Research and Quality.[7] Studies were graded as good (A), fair (B), or poor (C) quality based on the likelihood of biases and completeness of reporting. Grades for different outcomes could vary within the same study.

For each intervention, we generated an "evidence profile" by grading the quality of evidence for each outcome according to the Grades for Recommendation, Assessment, Development and Evaluation (GRADE) system. The process considered the methodologic quality, consistency of results across studies, directness of the evidence, and imprecision or sparseness of evidence

to determine an overall quality of evidence. Four quality rating categories were possible: high (A), moderate (B), low (C), and very low (D).[8]

We developed guideline statements incorporating the balance between benefits and harms of the compared interventions when the data were sufficient to support these statements. Each guideline statement was assigned an overall level of strength of the recommendation (1="strong," 2="weak") based on the quality of the supporting evidence and the size of the net benefit. The strength of a recommendation indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. The wording and its implications for patients, physicians, and policymakers are detailed in the "Conclusions."

RESULTS

The search identified 5,848 citations. Data were extracted and analyzed from the 26 studies that met all inclusion criteria for the systematic review (Fig. 1; Table 1).

Twenty-two studies included women predominantly with abnormal uterine bleeding presumed secondary to endometrial dysfunction.[9–30] Three studies[18,20,22] included both patients with abnormal uterine bleeding secondary to endometrial dysfunction (82%, 95%, 86%) and those with abnormal uterine bleeding secondary to ovulatory dysfunction (18%, 5%, 14%); these studies were included in the abnormal uterine bleeding presumed secondary to endometrial dysfunction category because the majority of patients fit this description. Seventeen of these studies required that patients objectively lose greater than 80 mL menstrual blood loss per cycle to be eligible for study participation.[11–16,19–24,26–30] Five studies included a levonorgestrel intrauterine system arm,[16,21,23,27,28] five studies included an OCP arm,[16,17,22,28,30] five studies included a luteal progestin arm,[9,12,20,23,26] one study included an extended oral progestin arm,[21] eight studies included an NSAID arm,[10,12–14,17–19,27] and seven studies included an antifibrinolytic arm (tranexamic acid, tranexamic acid prodrug, or epsilon amino caproic acid).[10,11,15,24–26,29] Studies ranged in quality, and the quality of individual studies is noted in Table 1. Sample sizes ranged from 16 to 304 participants.[11,29]

All 22 abnormal uterine bleeding presumed secondary to endometrial dysfunction studies reported on bleeding outcomes in terms of menstrual blood loss. All but one[9,32] calculated the change in menstrual blood loss quantitatively using the objective alkaline–hematin method,[10–30] the semiobjective pictorial blood assessment chart,[16,27,28,37] or both. Data are presented in Table 1.

Five abnormal uterine bleeding presumed secondary to endometrial dysfunction studies investigated the effectiveness of the levonorgestrel intrauterine system. All of these studies required participants to lose 80 mL or more menstrual blood loss per cycle at baseline to be eligible. Two of these

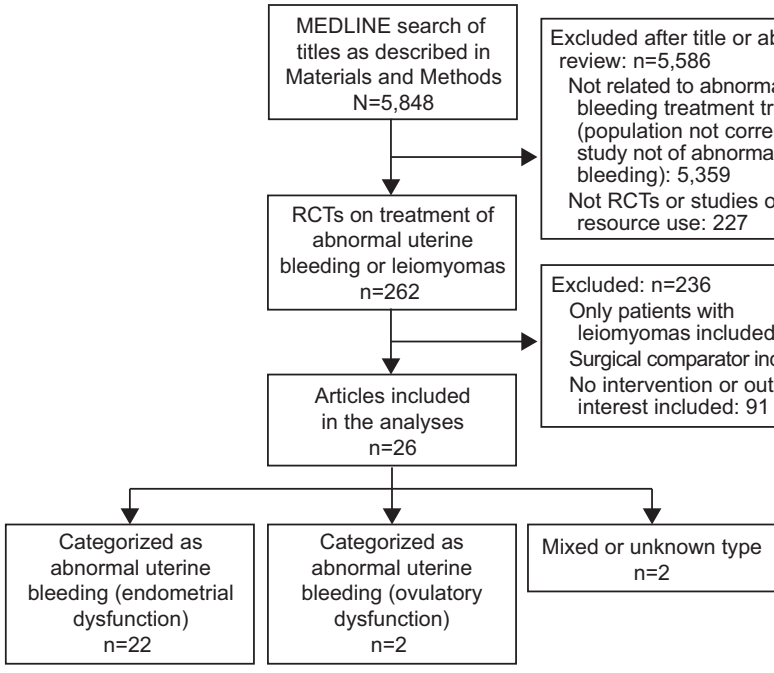

Fig. 1. Study selection process. Articles searched published between 1950 to May 14, 2012. RCT, randomized controlled trial.

Matteson. Nonsurgical Management of Heavy Menstrual Bleeding. Obstet Gynecol 2013.

Table 1. Summary of Studies, Comparators, Primary Outcomes, Sample Size, and Power: Nonsurgical

Study (author, year), Study Quality,* n	Intervention and Comparator(s)	Primary Outcome (No. of Months or Cycles of Treatment)	List of Other Outcomes Assessed
Population: abnormal uterine bleeding secondary to endometrial dysfunction			
Endrikat, 2009,[16] B, 42	LNG-IUS compared with OCPs	Mean blood loss†‡ (12 mo); LNG-IUS with greater reduction in mean blood loss compared with OCPs (83% compared with 68%, *P*=.002)	QOL
Irvine, 1998,[21] B, 44	LNG-IUS compared with oral progestin (extended)	Mean blood loss†‡ (3 mo); no difference in mean blood loss reduction detected between LNG-IUS and norethisterone groups (94% compared with 87%, nonsignificant, underpowered)	QOL, satisfaction, adverse events
Kaunitz, 2010,[23] B, 165	LNG-IUS compared with oral progestin (luteal)	Mean blood loss†§ (6 mo); LNG-IUS with greater reduction in mean blood loss compared with medroxyprogesterone acetate (71% compared with 22%, *P*<.001)	Adverse events
Reid, 2005,[27] B, 51	LNG-IUS compared with mefenamic acid	Mean blood loss†§ (six cycles); LNG-IUS with greater reduction in medroxyprogesterone acetate compared with mefenamic acid (95% compared with 23%, *P*<.001)	Adverse events
Shabaan, 2011,[28] B, 112	LNG-IUS compared with OCPs	Mean blood loss†§ (12 mo); LNG-IUS with greater reduction in mean blood loss compared with OCPs (87% compared with 35%, *P*=.013)	QOL
Fraser, 1991,[17] C, 45	Crossover study involving mefenamic acid, naproxen, OCPs, and danazol	Mean blood loss‡ (two cycles of mefenamic acid, two cycles no treatment, two cycles other treatment); significant reduction in mean blood loss seen with OCPs (43%, *P*<.001) and danazol (49%, *P*=.006); no within-group differences seen when comparing mefenamic acid with the other treatment; comparisons between groups not made	None
Fraser, 2011,[30] A, 231	OCPs compared with placebo	"Complete response" to therapy†§‖ (seven cycles); 40.7% of OCP group and 1.6% of placebo group with "complete response"; OCPs greater mean blood loss reduction (69.4% compared with 5.8%, *P*<.001)	Adverse events

(*continued*)

Table 1. Summary of Studies, Comparators, Primary Outcomes, Sample Size, and Power: Nonsurgical (*continued*)

Study (author, year), Study Quality,* n	Intervention and Comparator(s)	Primary Outcome (No. of Months or Cycles of Treatment)	List of Other Outcomes Assessed
Jensen, 2011,[22#] A, 190	OCPs compared with placebo	"Complete response" to therapy[†§‖] (seven cycles); 43.8% of the OCP group and 4.2% of placebo group with "complete response"; OCPs greater reduction in mean blood loss (64.2% compared with 7.8%, $P<.001$)	Adverse events
Bonduelle, 1991,[9] C, 30	Oral progestin (luteal) compared with danazol	Bleeding intensity score[‡] (three cycles); danazol with greater improvements in bleeding intensity score than norethisterone ($P<.02$); no significant improvement in bleeding intensity seen in norethisterone group	Pain, adverse events
Cameron, 1990,[12] B, 32	Oral progestin (luteal) compared with mefenamic acid	Mean blood loss[†‡] (two cycles); significant reduction in mean blood loss in both groups—67% with norethisterone and 52% with mefenamic acid (difference nonsignificant)	Pain, adverse events
Higham, 1993,[20] B, 54	Oral progestin (luteal) compared with danazol	Mean blood loss[†‡] (three cycles); norethindrone with a lesser reduction in mean blood loss than either danazol regimen (14% compared with 40% and 26%, $P=.043$ and $P=.017$, respectively)	None
Preston, 1995,[26] A, 46	Oral progestin (luteal) compared with tranexamic acid	Mean blood loss[†§] (two cycles); norethisterone resulted in an increase in mean blood loss and tranexamic acid resulted in a decrease in mean blood loss (20% increase compared with 45% decrease, $P<.001$)	QOL, sexual function, pain, adverse events
Bonnar, 1996,[10] A, 76	Tranexamic acid compared with mefenamic acid compared with ethamsylate	Mean blood loss[§] (three cycles); tranexamic acid with greater reduction in mean blood loss than mefenamic acid (54% compared with 20%, $P<.001$), both better than ethamsylate ($P<.001$); no reduction in bleeding seen with ethamsylate	Pain, adverse events
Callender, 1970,[11] B, 16	Tranexamic acid compared with placebo	Mean blood loss[†‡] (three cycles per treatment, crossover study); tranexamic acid with greater reduction in mean blood loss compared with placebo (38% compared with 6%, $P<.05$)	Adverse events

(*continued*)

Table 1. Summary of Studies, Comparators, Primary Outcomes, Sample Size, and Power: Nonsurgical (*continued*)

Study (author, year), Study Quality,* n	Intervention and Comparator(s)	Primary Outcome (No. of Months or Cycles of Treatment)	List of Other Outcomes Assessed
Edlund, 1995,[15] B, 91	Tranexamic acid (two types) compared with placebo	Mean blood loss†‡ (3 mo); reductions in mean blood loss with twice-daily dosing (41%) and four times a day dosing (33%) (difference nonsignificant), better than placebo ($P<.001$)	Adverse events
Freeman, 2011,[29] A, 304	Tranexamic acid (two doses) compared with placebo	Mean blood loss†§ (three cycles); greater reduction in mean blood loss with 1.3 g three times daily and 0.65 g three times daily (38.6% and 26.1%) compared with placebo (1.9%, $P<.001$)	QOL, adverse events
Lukes, 2010,[24] A, 196	Tranexamic acid compared with placebo	Mean blood loss†§ (six cycles); greater reduction in mean blood loss in tranexamic acid group (40.4%) than placebo (8.2%, $P<.001$)	QOL, adverse events
Nilsson, 1965,[25] B, 37	Epsilon amino caproic acid compared with placebo	Mean blood loss‡ (two cycles of each treatment, crossover); participants experienced a 62% decrease in mean blood loss when treated with epsilon amino caproic acid when compared with placebo ($P<.001$)	Adverse events
Chamberlain, 1991,[13] B, 44	Mefenamic acid compared with ethamsylate	Mean blood loss†‡ (three cycles); no difference detected between treatments; reduction in mean blood loss of 24% with mefenamic acid and 20% with ethamsylate	Adverse events
Dockeray, 1989,[14] A, 40	Mefenamic acid compared with danazol	Mean blood loss†‡ (two cycles); greater reduction in mean blood loss in danazol group than mefenamic acid group (60% compared with 20%, $P<.001$)	Pain, adverse events
Hall, 1987,[19] B, 40	Mefenamic acid compared with naproxen	Mean blood loss‡ (two cycles per treatment, crossover study); both treatments with significant reduction in mean blood loss from baseline (mefenamic acid 46–47%, naproxen 44–48%); no difference between groups	Adverse events
Fraser, 1981,[18¶] C, 85	Mefenamic acid compared with placebo	Mean blood loss‡ (two cycles per treatment, crossover study); significantly lower mean blood loss seen with mefenamic acid when compared with mean blood loss with placebo (mean blood loss 28% lower, $P<.001$)	Pain, adverse events

(*continued*)

Table 1. Summary of Studies, Comparators, Primary Outcomes, Sample Size, and Power: Nonsurgical (*continued*)

Study (author, year), Study Quality,* n	Intervention and Comparator(s)	Primary Outcome (No. of Months or Cycles of Treatment)	List of Other Outcomes Assessed
Population: abnormal uterine bleeding secondary to ovulatory dysfunction, mixed, uncertain			
Davis, 2000,[33] B, 201 (abnormal uterine bleeding secondary to ovulatory dysfunction)	OCPs compared with placebo	"Resolution of abnormal bleeding"[§] (three cycles); "investigator assessment of resolution" and "patient assessment of resolution" greater in OCP group (81% and 87%, respectively) than placebo (36% and 45%, respectively); $P<.001$ for both	Bleeding, QOL, sexual function
Cetin, 2009,[34] C, 58 (abnormal uterine bleeding secondary to ovulatory dysfunction)	OCPs compared with OCPs plus gonadotropin-releasing hormone agonist	Primary outcome unclear[‡] (6 mo); gonadotropin-releasing hormone plus group used fewer sanitary products than OCP alone group (47% compared with 52%, $P<.05$)	Bleeding, satisfaction, additional treatment, adverse events
Kucuk, 2008,[35] B, 132 (mixed)	LNG-IUS compared with oral progestin (continuous) compared with intramuscular DMPA	Pictorial blood loss assessment chart score[‡] and mean duration of menses in days[‡] (two cycles); no difference in duration of bleeding between groups; LNG-IUS with greater reduction in mean blood loss (73%) compared with medroxyprogesterone acetate (33%) and DMPA (49%); $P<.01$ for both; difference between medroxyprogesterone acetate and DMPA nonsignificant	Adverse events
Lahteenmaki, 1998,[36] C, 56 (uncertain)	LNG-IUS compared with "control" (not specified)	Decision to continue current therapy versus hysterectomy[§] (6 mo); greater proportion in LNG-IUS group cancelled hysterectomy (64% compared with 14%, $P<.001$)	Bleeding, QOL, sexual function

LNG-IUS, levonorgestrel intrauterine system; OCP, oral contraceptive pill; QOL, quality of life; DMPA, depot medroxyprogesterone acetate.

* Study Quality Rating determined by rating the quality of the study, the quality of the assessment of the particular outcome, the consistency of results across studies, the directness (applicability of results to population of interest), imprecision, and sparseness of evidence. A=good quality: no obvious biases or reporting errors, complete reporting of data; B=fair quality: problems with study or paper unlikely to cause major bias; C=poor quality: cannot exclude possible significant biases, poor methods, incomplete data, reporting errors.

† Greater than 80 mL mean blood loss at baseline required for study eligibility.

‡ Study either not powered to detect a difference in the outcome or no power calculation described.

§ Study powered to detect difference in this outcome.

‖ Outcome: complete response to therapy defined by a composite of absence of all qualifying conditions.

Mixed population with mean blood loss greater than 80 mL. Ninety-five percent with "regular menses" therefore included in the abnormal uterine bleeding secondary to endometrial dysfunction group for analyses.

¶ Mixed population with 82% abnormal uterine bleeding secondary to endometrial dysfunction and 18% abnormal uterine bleeding secondary to ovulatory dysfunction included in the abnormal uterine bleeding secondary to endometrial dysfunction group for analyses.

compared the levonorgestrel intrauterine system with OCPs and found that at 12 months, decrease in menstrual blood loss was significantly greater using the levonorgestrel intrauterine system (83% compared with 68%, $P=.002$ and 87% compared with 35%, $P=.013$).[16,28] The levonorgestrel intrauterine system resulted in significantly greater blood loss reduction than luteal-phase oral progestin[23] and the NSAID,

mefenamic acid.[27] Irvine et al compared the levonorgestrel intrauterine system with extended oral progestin; both treatment groups showed significant reductions in menstrual blood loss at 3 months (94% compared with 87%), but no difference was detected between groups.[21] However, based on the sample size calculation, the study was underpowered. Across studies, the levonorgestrel intrauterine system resulted in a 71–95% reduction in menstrual blood loss.

In addition to being compared with the levonorgestrel intrauterine system, OCPs were also directly compared with mefenamic acid[17] and with placebo.[22,30] Both mefenamic acid and OCPs reduced menstrual blood loss (38% and 43%, respectively) but the difference between groups was not significant.[17] Two similar trials showed that OCPs resulted in a greater reduction in menstrual blood loss compared with placebo.[22,30] Across studies, women treated with OCPs experienced a 35–69% reduction in menstrual blood loss.

Luteal-phase oral progestins (administered for 7–10 days per month) have been compared with the levonorgestrel intrauterine system,[23] tranexamic acid,[26] and NSAIDs.[12] Although tranexamic acid use resulted in a 45% reduction in menstrual blood loss over two cycles, luteal-phase oral progestins resulted in a 20% increase in menstrual blood loss ($P<.001$). When this same regimen of oral progestin was compared with mefenamic acid, both treatment groups demonstrated significant reductions in blood loss from baseline over two cycles (67% and 52%, respectively) but were not significantly different from each other (n=32).[12] Across studies, women treated with luteal-phase oral progestins experienced a 20% increase to 67% decrease in menstrual blood loss.

In addition to head-to-head comparison with luteal-phase oral progestin (above),[32] tranexamic acid (an antifibrinolytic) has been compared with mefenamic acid and with placebo.[10,11,15,24,25,29] Tranexamic acid had a superior reduction in menstrual blood loss over three cycles compared with mefenamic acid (54% compared with 10%, $P<.001$).[10] Antifibrinolytics were compared with placebo and in studies, cases were superior for the reduction of blood loss.[11,15,24,25,29] Across studies, tranexamic acid use resulted in a 26–54% reduction in menstrual blood loss.

Comparisons of NSAIDs with other relevant interventions are described previously.[10,12–14,17,27] Mefenamic acid was also compared with placebo[18] and another NSAID (naproxen sodium).[19] Mefenamic acid use resulted in significantly greater reduction in blood loss than placebo.[18] Although both mefenamic acid and naproxen sodium demonstrated reductions in blood loss compared with baseline, there were no significant differences between the two.[19] Across studies, women treated with mefenamic acid experienced a 10–52% reduction in menstrual blood loss.

Synthesizing these studies by generating "evidence profiles" as detailed in the "Methods" section, we found net benefits for levonorgestrel intrauterine system when compared with OCPs, luteal-phase progestins, and mefenamic acid for the reduction of menstrual blood loss in women with abnormal uterine bleeding secondary to endometrial dysfunction (moderate quality evidence). Moderate quality evidence also suggested net benefits to the use of OCPs and antifibrinolytics over placebo. Low-quality evidence suggested net benefits to the use of NSAIDs over placebo. We also found net benefits for the use of antifibrinolytics over luteal-phase oral progestins (very low quality evidence) and NSAIDs (moderate quality evidence) for the reduction of menstrual bleeding. Based on the available literature, we could not determine whether there was a difference between OCPs and NSAIDS or luteal progestins and NSAIDs.

Other outcomes of interest for this systematic review were either reported infrequently or inconsistently across 11 studies involving women with presumed abnormal uterine bleeding presumed secondary to endometrial dysfunction. Quality of life was measured in six studies,[16,21,24,26,28,29] sexual function in one study,[26] satisfaction in one study,[21] pain in six studies,[9,10,12,14,18,26] and additional treatment in no studies. For these studies, evidence profiles were generated and data were summarized. Because of the limited number of studies and the limited quality of the outcomes, clinical practice guidelines for these outcomes were not generated.

Treatment with both the levonorgestrel intrauterine system and OCPs was associated with QOL improvement. Although treatment with levonorgestrel intrauterine system resulted in greater QOL improvements initially, this difference was not observed at 1 year.[16] Tranexamic acid was shown to improve both physical function and social function QOL outcomes.[24,26,29] No QOL improvements were reported for luteal-phase progestins.[26] With respect to pain, significant improvement was reported for patients with dysmenorrhea using NSAIDs and tranexamic acid,[15,18] whereas luteal-phase progestin and tranexamic acid did not reach significance in one study.[26] Luteal-phase progestin, tranexamic acid, and NSAIDs may favorably affect abdominal pain and back ache.[9,12,26]

Only two studies included women predominantly with abnormal uterine bleeding secondary to ovulatory dysfunction[33,34] and two studies had "mixed or uncertain" etiologies of abnormal uterine bleeding.[35,36]

Therefore, evidence profiles were not generated for these populations. The main results of these four studies are summarized in Table 1.

Twenty of the 26 studies reported on adverse events. Adverse events were inconsistently ascertained, recorded, and reported and therefore could not be tabulated or compared between interventions or studies. To highlight the inconsistency in reporting across studies, for the adverse event "bloating or weight gain," one study reported a prevalence of 67% among participants using luteal oral progestin,[9] whereas two other studies using the same intervention reported a prevalence that ranged from 0% to 6%.[23,26]

CONCLUSION

Abnormal uterine bleeding is a prevalent symptom among women seeking gynecologic care. Based on available RCTs, we found that the levonorgestrel intrauterine system, OCPs, extended-cycle oral progestins, tranexamic acid, and NSAIDs were all effective treatments for the reduction of menstrual blood loss in women with abnormal uterine bleeding presumed secondary to endometrial dysfunction and that the levonorgestrel intrauterine system, OCPs, and antifibrinolytics were all superior to luteal-phase progestins. We were unable to make other definitive conclusions on the effectiveness of these commonly used treatments relative to one another for other essential outcomes (QOL, sexual function, pain, satisfaction, additional treatment, or adverse events) or for other populations (abnormal uterine bleeding presumed secondary to ovulatory dysfunction or mixed populations) because of limited RCTs, limited reporting on these outcomes, or suboptimal data quality obtained within available studies.

Based on the evidence, the Society of Gynecologic Surgeons' Systematic Review Group developed Clinical Practice Guidelines for nonsurgical treatment for abnormal uterine bleeding. Guidelines were only developed for the outcome of "reduction in menstrual bleeding" for populations of women with abnormal uterine bleeding presumed secondary to endometrial dysfunction (heavy and regular bleeding), because this was the only population and outcome for which there was enough good-quality data to generate meaningful guidelines (Table 2). Each Clinical Practice Guideline received a "grade" in two parts: 1) the strength of the recommendation (1="we recommend" or 2="we suggest"); and 2) the quality of the evidence (A, B, C, D). Based on the quality of the evidence for individual comparisons, some of our guideline statements are presented as recommendations and others are presented as suggestions.

The strengths of this study are the comprehensive nature of the literature review and the clear and standardized methodology used for guideline development. Since the Guidelines on Heavy Menstrual Bleeding published by the National Institute of Clinical Excellence in the United Kingdom 5 years ago,[31] nine new RCTs on nonsurgical treatments for abnormal uterine bleeding have been published and were included in our review, therefore providing new evidence toward clinical practice guidelines.[16,22–24,28–30,34,35] A national survey of U.S. gynecologists suggested that obstetricians and gynecologists in the United States may not be accessing lengthy evidence-based reviews such as those conducted by the National Institute of Clinical Excellence and the Cochrane collaboration.[6] Additionally in that study, only 23% of respondents were aware that luteal-phase progestins were ineffective treatments for abnormal uterine bleeding secondary to endometrial dysfunction.[6] It is our hope that our more concise review will further disseminate the evidence on effective treatments for abnormal uterine bleeding and help to improve the management of women with this symptom.

In clinical practice, the diagnosis, evaluation, and treatment of heavy menstrual bleeding are based on "patient experience," the woman's personal assessment of her blood loss, and its effect on her life.[38] A limitation of our study is that it falls short for making suggestions and guidelines for the outcomes likely most meaningful for women: "patient experience" and bleeding-related QOL because, traditionally, research on heavy menstrual bleeding has focused on measured menstrual blood loss as the main study outcome.[39] Other limitations include difficulty determining the exact study population and the effect of sponsorship and publication bias on the body of literature. Nineteen of the 26 studies were sponsored or conducted by the treatment's manufacturer.

We reviewed RCTs on seven different nonsurgical treatments for abnormal uterine bleeding secondary to endometrial dysfunction and abnormal uterine bleeding secondary to ovulatory dysfunction. A limitation of our conclusions is that they are based on relatively few RCTs and that women who participate in RCTs may differ from the population of women experiencing abnormal uterine bleeding. Despite the number of treatments available and the prevalence of abnormal uterine bleeding, we identified only 26 RCTs comparing these treatments, resulting in sparse comparisons between most interventions, and only two of these studies specifically addressed women with abnormal uterine bleeding presumed secondary to ovulatory dysfunction. Given

Table 2. Medical Management of Abnormal Uterine Bleeding

Intervention A	Intervention B	Preferred Intervention (Level of Evidence)	Clinical Practice Guideline Statements for the Reduction in Mean Blood Loss
LNG-IUS	OCPs	LNG-IUS (1B)	We recommend the use of LNG-IUS over OCPs, luteal-phase progestins, and NSAIDs
	Luteal oral progestin	LNG-IUS (1B)	
	Extended oral progestin	Either (2C)	
	Antifibrinolytics	No direct comparison*	
	NSAID	LNG-IUS (2C)	
OCPs	LNG-IUS	LNG-IUS (1B)	We recommend the use of LNG-IUS over OCPs; we suggest the use of OCPs over luteal-phase progestins
	Luteal oral progestin	No direct comparison*	
	Extended oral progestin	No direct comparison*	
	Antifibrinolytics	No direct comparison*	
	NSAID	Insufficient data† (2D)	
Luteal-phase oral progestin	LNG-IUS	LNG-IUS (1B)	We recommend the use of LNG-IUS over luteal-phase progestins; we suggest the use of OCPs and antifibrinolytics over luteal-phase progestins
	OCPs	No direct comparison*	
	Extended oral progestin	No direct comparison*	
	Antifibrinolytics	Antifibrinolytic (2D)	
	NSAID	Insufficient data (2C)	
Extended cycle oral progestin	LNG-IUS	Either (2C)	There are insufficient data on which to make suggestions
	OCPs	No direct comparison*	
	Luteal oral progestin	No direct comparison*	
	Antifibrinolytics	No direct comparison*	
	NSAID	No direct comparison*	
Antifibrinolytics	LNG-IUS	No direct comparison*	We suggest the use of antifibrinolytics over luteal-phase progestins and NSAIDs
	OCPs	No direct comparison*	
	Extended oral progestin	Antifibrinolytic (2D)	
	Luteal oral progestin	No direct comparison*	
	NSAID	Antifibrinolytic (1B)	

LNG-IUS, levonorgestrel intrauterine system; OCP, oral contraceptive pill; NSAID, nonsteroidal anti-inflammatory drug.

Clinical Practice Guidelines for the reduction in menstrual bleeding: For the reduction in mean blood loss in women with heavy menstrual bleeding presumed secondary to abnormal uterine bleeding–endometrial who desire medical therapy and have no contraindications nor objection to the use of interventions A or B. (Abnormal uterine bleeding–endometrial as defined by the International Federation of Gynecology and Obstetrics classification system.[3])

* No studies reviewed included a direct comparison of treatment A with B.

† Data are available for these comparisons (A compared with B) but are insufficient to recommend A or B for control of bleeding.

the prevalence of abnormal uterine bleeding and the possibility that treatments that are effective for abnormal uterine bleeding secondary to endometrial dysfunction may not be effective for abnormal uterine bleeding secondary to ovulatory dysfunction, more research on this population is necessary. In addition, of these 26 studies, 17 (65%) included menstrual blood loss greater than 80 mL as an eligibility criteria for participation in the study, which may not be applicable to the general population of women seeking treatment for heavy menstrual bleeding.[38] Including women who self-report abnormal uterine bleeding in studies and measurement of bleeding-related QOL as a main outcome should be high priorities of research in this area. Also, some treatments have not yet been compared in head-to-head clinical trials, so it is unknown which treatments are most effective.

Abnormal uterine bleeding is a prevalent symptom that has an enormous effect on the QOL of women and health care costs. This review provides a concise distillation of the available evidence on nonsurgical treatment for this important problem that gynecologists treat on a regular basis. Although there are limitations to the body of literature on this symptom, this review and clinical practice guidelines provide up-to-date information on the relative effectiveness of abnormal uterine bleeding treatments commonly used in clinical practice and will assist with clinical decision-making and setting priorities for research on this important symptom.

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