Effective Health Care Program

Comparative Effectiveness Review
Number 96

Primary Care Management of Abnormal Uterine Bleeding

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Primary Care Management of Abnormal Uterine Bleeding

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Primary Care Management of Abnormal Uterine Bleeding

Structured Abstract

Objective. The Vanderbilt Evidence-based practice Center systematically reviewed evidence about interventions for symptomatic abnormal uterine bleeding (AUB), both irregular and cyclic. We focused on interventions that are suitable for use in primary care practice including medical, behavioral, and complementary and alternative medicine approaches.

Data sources. We searched MEDLINE®, CINAHL®, and Embase for randomized controlled trials (RCTs) published in English from January 1980 to June 2012 in women with symptomatic AUB. We also searched regulatory data and scientific publications for data about harms.

Review methods. Using dual review with a priori criteria, we excluded 1,734 publications because they did not address a Key Question, were not an eligible study design, or did not apply to the primary care treatment of AUB.

Results. Thirty-nine RCTs (6 good quality, 10 fair quality, and 23 poor quality) evaluated 12 distinct interventions. These included 7 studies of the levonorgestrel-releasing intrauterine system (LNG-IUS), 13 of nonsteroidal anti-inflammatory drugs (NSAIDs), 6 of tranexamic acid (TXA), and 5 of combined oral contraceptive pills (COCs). The majority of studies made direct comparisons to other drugs. Ten studies enrolled women with irregular uterine bleeding; the remainder focused on women with heavy cyclic bleeding. Among women with irregular menses, metformin, metformin with exenatide, and a tricyclic oral contraceptive improved menstrual regularity. Among women with heavy, cyclic menstrual bleeding all seven studies of LNG-IUS favored the intrauterine system in comparisons that included NSAIDs, COCs, progestogens and usual care. Reduction in menstrual blood loss ranged from 70 to 87 percent less bleeding than baseline. NSAIDs reduced bleeding in six of six studies when compared with placebo or progestogens. The degree of improvement was highly variable for individual women. TXA was more effective than progestogens and NSAIDs in three of four studies, and COCs provided benefit compared with placebo in two studies. Harms were rare and trials underpowered to assess harms for all interventions. For most interventions, surveillance studies of longer-term risks were not done in comparable populations.

Conclusions. Two interventions for irregular bleeding (metformin, COCs) and four for heavy cyclic bleeding (LNG-IUS, NSAIDs, TXA) have low or moderate strength of evidence for effectiveness, while COCs have high strength of evidence. Several common interventions (including diet and exercise and acupuncture) lack sufficient evidence. Across interventions, data are sparse to evaluate long-term improvements and risk of harms.
Limitations include a predominance of small, short trials lacking standard terminology and diagnostic criteria for identifying and including women with AUB. Tools for collecting outcome data are crude (e.g., collection of sanitary products to measure blood loss) and may contribute to a high rate of attrition. Emphasis on biologic outcomes may neglect the importance of patient-reported outcomes that assess whether symptoms are considered resolved by women themselves.

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Executive Summary

Background

Abnormal uterine bleeding (AUB) is among the most common gynecologic complaints of reproductive-age women in ambulatory care settings. It is estimated to affect 11 to 13 percent of reproductive-age women at any given time. Prevalence increases with age, reaching 24 percent in women aged 36 to 40.[1,2] Women generally present for care because the amount, timing, or other characteristics of the bleeding have changed from their individual norm. Population norms for menstrual bleeding, as established by 5th and 95th percentiles, are:[3-7]

- Frequency of menses within a 24- to 38-day window
- Regularity (i.e., cycle-to-cycle variation) within 2 to 20 days
- Duration of flow from 4 to 8 days
- Blood loss volume from 5 to 80 ml

Symptoms outside this normal range, or different from normal for the individual, can become problematic and deserve evaluation because they can warn of underlying conditions. Common problems include worry about the cause, embarrassment if the bleeding includes flooding-type bleeding with saturation of clothing, missed work and responsibilities, limitations of social activities and exercise, decreases or changes in sexual activity, and frustration with costs of sanitary protection. Collectively, the effects of troublesome bleeding reduce quality of life and drive desire for information about causes and treatment options.[1,8]

There is not a clear consensus on the clinical evaluation of a patient presenting with abnormal bleeding. Recommendations suggest that initial evaluation confirm the source and timing of bleeding, and exclude certain architectural etiologies (e.g., fibroids, polyps), cancer and precancerous changes in the cervix or uterus, coagulation defects, and systemic disease. The 2011 International Federation of Gynecology and Obstetrics (FIGO) classification recommends a structured history followed by uterine evaluation.[9] In the research setting, the alkaline hematin method is the preferred technique for direct measurement of total menstrual blood loss (MBL). The pictorial blood loss assessment chart is a semi-quantitative tool for uniform reporting of bleeding as represented by the degree of saturation of sanitary pads and tampons. Diagnostic tools and evaluation strategies are not within the scope of this review;[10,11] however, the review captures the operational definitions used by researchers and addresses applicability of the findings to contemporary practice.

Terminology

Nomenclature to classify AUB has evolved steadily over the past several decades.[12] Early classifications relied primarily on bleeding characteristics, using terms like menorrhagia (i.e., abnormally long or heavy menses) and metrorrhagia (i.e., bleeding at irregular intervals). These terms were often linked with timing and amount to infer whether or not regular and predictable ovulation was occurring. These terms are generally applied without formal documentation of ovulatory status. Furthermore, previously applied terms like “dysfunctional uterine bleeding” also carried a variable element of recognition that the label was a diagnosis of exclusion.[12] The resulting challenge was that practitioners and researchers applied different exclusions before selecting interventions or enrolling patients. Over time, these differences in terminology and use of operational definitions resulted in inconsistent application of diagnostic terms.[4,12-14]

Recent international consensus recommendations, formally adopted by FIGO in 2010 and published in 2011, more consistently align terminology by creating two major groupings (i.e., discrete structural vs. nonstructural) for causes of bleeding.[9,15,16] The FIGO classification includes nine categories of abnormal bleeding arranged according to the acronym PALM-COEIN:[9,15] four have objective visual criteria detected by imaging, biopsy, or pathology (i.e., PALM: **p**olyps; **a**denomyosis; **l**eiomyomata; and **m**alignancy and hyperplasia) while another five are not directly related to structural abnormalities (i.e., COEIN: **c**oagulopathy; **o**vulatory dysfunction; **e**ndometrial; **i**atrogenic; and **n**ot yet classified).

If we map the intended focus of this comparative effectiveness review to the FIGO classification, we are addressing the COEIN groups that are characterized as "ovulatory dysfunction" (AUB-O), "endometrial hemostatic dysfunction" (AUB-E), and "not yet classified" (AUB-N) abnormal bleeding. However it is crucial to note that direct measures of ovulation are not employed in most available literature and endometrial samples for classification are even rarer, except when used to rule out malignancy. Indeed much remains to be explained about the pathophysiology of the very common and problematic complaint of unpredictable and/or heavy bleeding. In summary, the relevant population for this review includes nonpregnant women from menarche to menopause who have had abnormal bleeding (scant or heavy) for 3 months or longer that is not attributed to structural abnormalities, coagulation defects, systemic illnesses, or medications.

While some reviews further subdivide women experiencing AUB into age groups,[17] such as those near menarche and in the perimenopausal timeframe, we plan to retain an emphasis on categorization. Women across the reproductive lifespan can have abnormal bleeding that arises from ovulatory dysfunction or endometrial processes.[18] While the underlying causes may vary, for instance from lack of consistent regulation of the hypothalamic-pituitary-ovarian axis in teens near the onset of menses, and from lack of ovarian reserve in perimenopausal women, the treatment options overlap.[19] We will report when research was done with an age-restricted population but will otherwise cover all the relevant literature regardless of reproductive age or reproductive history of participants.

Therapies

In a recently published research article examining the practice patterns for medical treatment of AUB, authors reported that practicing obstetrician-gynecologists most frequently selected oral contraceptives for the treatment of both irregular and abnormal cyclic menstrual bleeding and lacked an overall awareness of current evidence on effectiveness of treatment options for AUB.[20]

Current recommendations for medical management of irregular and abnormal cyclic uterine bleeding include levonorgestrel-releasing intrauterine system (LNG-IUS), nonsteroidal anti-inflammatory drugs (NSAIDs), antifibrinolytics, combined oral contraceptives (COCs), and progestogens.[21-26] Surgical intervention is usually reserved for women with persistent bleeding that does not respond to medical therapy or for women who have finished childbearing and do not wish to indefinitely continue medical therapy.[2,21]

Scope and Key Questions

The relevant population for this review includes nonpregnant women from menarche to menopause who have had AUB for 3 months or longer, that is not attributed to structural abnormalities, coagulation defects, systemic illnesses, or medications. This review evaluates the interventions and direct comparisons among treatments that are often used and promoted as first-

line choices, with the goal of clearly describing their effectiveness and potential harms for use in primary care settings. We explicitly defined eligibility criteria using a PICOTS (population, intervention, comparator[s], outcome, timing, and setting) structure (Table A).

Table A. PICOTS

PICOTS Element	Description
Population:	Nonpregnant women from menarche to menopause who have had abnormal bleeding for 3 months or longer whose bleeding is not caused by structural abnormalities, coagulation defects systemic disease, cancer, or medication. Two specific subtypes of abnormal bleeding will be the focus: • *Irregular uterine bleeding:* problem bleeding (frequent or infrequent) of 3 months or greater duration, excluding regular cyclic/menstrual patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, coagulation defects, and related systemic disease. • *Abnormal cyclic uterine bleeding*: problem bleeding of 3 months or greater duration, excluding irregular and unpredictable patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, coagulation defects, and related systemic disease.
Interventions:[a]	• Medical therapies o Nonsteroidal anti-inflammatory drugs o Antifibrinolytics o Oral hormone treatments (e.g., oral contraceptives, progestogens) o Levonorgestrel-releasing intrauterine system o Vaginal ring contraceptive device • Behavioral strategies (e.g., stress reduction, weight reduction, exercise) • Complementary and alternative medicine therapies (e.g., acupuncture, herbal medicine)
Comparator:	Direct comparison among interventions listed above or comparison to placebo.
Outcomes:	• Bleeding profile (e.g., amount, frequency, duration, pattern, symptom bother, hematocrit) • Quality of life including both general and bleeding specific measures • Pain related to bleeding • Sexual function as reported by sexual function measures, general measures of sexual activity, frequency and satisfaction • Patient satisfaction with outcomes and acceptability of treatment • Fertility • Time to conception • Additional interventions including concurrent and consecutive surgical and nonsurgical treatments • Harms[b] (e.g., thromboembolic events, emotional side effects, weight gain, short- and long-term harms)
Timing:	Interventions initiated after symptoms present most months for 3 months or longer.
Setting:	Any clinical care setting.

PICOTS = population, intervention, comparator, outcome, timing, and setting
[a]Excluding surgical interventions and procedures such as endometrial ablation.
[b]Includes treatment-related adverse events (e.g., drug side effects); does not include consequences related to the failure to adequately treat the symptom.

Key Questions

Key Question 1A

What is the evidence for the effectiveness of medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) for improving short and long-term outcomes in women with irregular uterine bleeding?

Key Question 1B

What is the evidence for the effectiveness of medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) for improving short and long-term outcomes in women with abnormal cyclic uterine bleeding?

Key Question 2

What are the harms, including adverse events, associated with medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) in women with irregular uterine bleeding or abnormal cyclic uterine bleeding?

Analytic Framework

We developed the analytic framework (Figure 1 of full report) based on clinical expertise of Key Informants and refined it with input from a Technical Expert Panel. The analytic framework illustrates the population, interventions, outcomes, and adverse effects that guided the literature search, study eligibility, screening, and synthesis.

Methods

Literature Search

For Key Question (KQ) 1, we searched MEDLINE®, CINAHL®, and Embase. Search results were limited to papers published in English, and published in or after 1980. Search strategies used a combination of subject headings (i.e., controlled vocabulary) and keywords (Appendix A of full report). We also searched the reference lists of included publications and recent systematic reviews related to management of AUB. For KQ2, we expanded our search of primary literature to include standard drug package inserts, and structured a separate literature search to identify publications that conducted surveillance for harms in large datasets (Appendix A of full report).

Inclusion and Exclusion Criteria

We predefined inclusion and exclusion criteria related to the study population, intervention, comparators, outcomes, timing, and setting in order to assess the eligibility of the search results. Eligible studies had to explicitly define and describe the study population, interventions, and outcomes. We included randomized controlled trials (RCTs) of interventions for women with irregular or abnormal cyclic uterine bleeding. We excluded studies of women with AUB caused by coagulation defects, systemic disease, structural abnormalities, cancer, or medication side-effects. For KQ1A we included studies of women with polycystic ovarian syndrome (PCOS) if the patient baseline and outcome data included information on cycle regularity. We excluded studies of women with infertility if the primary treatment goal was conception. Harms data to address KQ2 was captured from the included RCTs for KQ1, reports based on pharmacoepidemiological databases, large observational studies, large case-controlled studies, and postmarketing surveillance data.

Study Selection

We developed screening forms to assess eligibility for inclusion in the review for KQ1 and KQ2. We revised the forms following testing by the team. We conducted screening in two phases: abstract and full-text screening. Publications were promoted to full-text review when one reviewer indicated that the publication met all inclusion criteria or when the title and abstract did not provide adequate information to make a determination. Two reviewers independently reviewed each publication at the full-text screening phase. Discordant classifications were resolved in team meetings including senior investigators.

Data Extraction

Two reviewers independently extracted relevant data from all included publications using a predefined evidence table shell. A senior investigator reviewed the evidence tables for accuracy and completeness. The final evidence tables are provided in Appendix J of the full report.

Quality (Risk of Bias) Assessment

We assessed quality of RCTs using the Cochrane Collaboration Risk of Bias Tool,[27] which evaluates domains including sequence generation, allocation concealment, blinding, outcome data reporting, and reporting bias. Two independent reviewers assessed risk of bias as low, high, or unclear for each domain. We used a preestablished threshold of criteria to rate the quality of each study based on the risk of bias assessment as good, fair, or poor. Discordant assessments were resolved in team meetings including senior investigators. A summary of all component items and overall risk of bias/quality score for each included study is provided in Appendix I of the full report.

Data Synthesis

We provide a systematic narrative synthesis of the available data from original research studies of acceptable quality for nonsurgical treatment of AUB. We present individual study data grouped by KQ and then intervention. Detailed study information is provided in evidence tables included in Appendix J of the full report.

A meta-analysis was not feasible for this review. Few studies had comparable treatment doses, interval, or duration of followup. Among those that did, the ability to aggregate data is limited by differences in outcomes measures which included measures of blood loss from sanitary product collection, and self-report using scoring systems including standardized pictorial systems. For regularity of bleeding no two measures of outcome were the same.

Strength of the Body of Evidence

For KQ1, we used explicit criteria to grade the overall strength of the evidence (e.g., low, moderate, high, and insufficient) on each intervention. We used established concepts of the quantity of evidence (e.g., numbers of studies, aggregate ending-sample sizes), the quality of evidence (i.e., from the quality ratings of individual articles), directness of the outcomes for informing the KQs, and the coherence or consistency of findings across similar and dissimilar studies and in comparison to known or theoretically sound principles of clinical or behavioral research and practice. For KQ2, we did not rate of strength of evidence because a fully inclusive

assessment of harms could not be completed for each of the 12 interventions that have been widely studied in populations that lack direct applicability to this report.

Applicability

We assessed applicability of the results from the literature to the population of women with abnormal cyclic and irregular uterine bleeding. Using the PICOTS framework, we identified factors that may limit the applicability of individual research studies. We summarized the applicability of the body of evidence and described key elements from the PICOTS framework that characterize the applicability of the identified studies.

Results

For KQ1, we identified 1,775 titles and abstracts for screening; 219 publications were identified as potentially eligible for inclusion and were promoted for full-text review. We identified 41 publications from 39 unique studies that met criteria for inclusion. Ten studies included in the review addressed KQ1A; 31 publications representing 29 studies addressed KQ1B. We conducted a separate search and screening process for KQ2. We identified 2,730 titles and abstracts for screening. Of these, 788 references were promoted for full text review. Using predefined criteria, we found 25 publications about harms that were eligible for inclusion. We obtained package inserts for each KQ1 included drug intervention.

Description of Included Studies (KQ1)

Thirty-nine included studies evaluated NSAIDs (13 studies),[28-40] the LNG-IUS (7 studies),[28,41-46] tranexamic acid (TXA; 7 studies),[29,34,40,47-50] COCs (6 studies),[31,41,43,51-53] contraceptive vaginal ring (1 study),[54] metformin (4 studies),[55-58] progestogens (1 study),[59] cabergoline (1 study),[60] lifestyle/behavioral changes (2 studies),[61,62] acupuncture (2 studies),[61,63] and patient decision aids (3 studies)[64-66] using at least one comparator or placebo arm. The total number of interventions addressed is greater than the number of studies because of direct comparisons between one or more interventions within single studies. Study duration was typically 6 months or less. Four of the studies addressing KQ1B included a followup of 1 to 2 years.

KQ1A. Management of Irregular Uterine Bleeding

Ten RCTs addressed restoring menstrual regularity in those with irregular uterine bleeding. Three were conducted in the United States,[51,57,62] two in Italy,[56,60] two in Turkey,[58,59] and one each in China,[63] Sweden,[61] and the United Kingdom.[55] The studies ranged in size from 23 to 201 participants and examined the efficacy of metformin (4 studies),[55-58] progestogen (1 study),[59] triphasic birth control pills (1 study),[51] cabergoline (1 study),[60] diet and exercise (1 study),[62] and acupuncture (2 studies).[61,63] The majority compared treatment to placebo or sham intervention; three included comparisons of effectiveness of two interventions. Two studies were classified as good quality,[51,60] two studies as fair quality,[55,63] and six studies as poor quality.[56-59,61,62]

Metformin and Exenatide

Metformin was an active treatment arm in four RCTs conducted among women with PCOS. Two RCTs compared metformin outcomes to a placebo group,[55,56] one compared metformin to N-acetyl-cysteine,[58] and one three-armed study compared metformin only, exenatide only, and

both.[57] In each case, compared with baseline or placebo, metformin was effective for improving the regularity of bleeding over a number of months.[55,56,58] Combination therapy improved cycle frequency better than metformin or exenatide alone in 60 women with PCOS.[57]

Progestogens

Vaginal micronized progesterone and oral dydrogesterone were studied in a single trial among women clinically classified as having dysfunctional uterine bleeding.[59] Both routes of administration improved cycle regularity with 92 percent and 85 percent of participants, respectively, achieving cycle length of less than 35 days and no intermenstrual bleeding by the third cycle of use. Effects were statistically comparable, but the trial was not powered to show equivalence or noninferiority.

COCs

A triphasic oral contraceptive was also studied in a single RCT among women with irregular uterine bleeding.[51] This trial included women with both short and long intervals between bleeding episodes and with both heavy and normal amounts of bleeding. The outcomes are provided by the authors in aggregate and not presented by initial bleeding characteristics. Overall, 68 percent of women taking the COC achieved excellent or good cycle control as assessed by the study investigators compared with 26 percent of those receiving a placebo.

Cabergoline

In a very preliminary investigation of cabergoline,[60] a drug indicated for the treatment of prolactinoma, treatment over 6 months was associated with return of regular menses in three of eight women compared with none of six receiving placebo. Women in the study had PCOS and normal prolactin levels.

Behavioral and Lifestyle Interventions

Among adolescents with PCOS, both a low-fat, calorie-restricted diet and a carbohydrate-restricted diet in conjunction with 30 minutes of aerobic activity 3 days a week resulted in more regular menses among those who lost weight.[62] This single small study did not present outcomes by the diet group to which participants were randomized. Presumably there was not a clear difference, meaning there is no evidence for which dietary approach to choose. A single trial of acupuncture in 84 women[61] also included an exercise control group at the same intensity as the diet and exercise trial. This group experienced a meaningful improvement in their menstrual frequency (42% increase from baseline calculated by study investigators) that was comparable to acupuncture at 32 weeks. We did not find evidence comparing diet to exercise directly.

Complementary and Alternative Medicine

Two studies of acupuncture with different underlying hypotheses and different methods (conventional acupuncture and low-frequency electroacupuncture) found benefit for a specific style of acupuncture when compared with no intervention or alternate placement of acupuncture needles.[61,63] By 32 weeks in the trial of electroacupuncture for PCOS,[61] women who received 14 acupuncture treatments over 16 weeks had a 121 percent improvement in cycle regularity while those who exercised only had a 42 percent improvement. Both were statistically comparable in this small trial. Both acupuncture and exercise were superior to no treatment. In the trial of two differing placements of needles every other day for 3 cycles,[63] women who received treatment

for “mind tranquilizing and menstruation promotion” had greater improvements (no treatment failures among 21 women) compared with those receiving traditional placement (n=16) for “delayed menses” among whom 19 percent did not have improvements.

KQ1B. Management of Abnormal Cyclic Bleeding

We identified 31 publications representing 29 studies addressing nonsurgical interventions for the management of abnormal cyclic uterine bleeding. The interventions evaluated in the studies included the LNG-IUS (7 studies),[28,41-46] NSAIDs (13 studies),[28-40] TXA (7 studies),[29,34,40,47-50] COCs (5 studies),[31,41,43,52,53] and contraceptive vaginal ring (1 study).[54] We also identified three studies that evaluated decision aids for the management of AUB.[65-67] Included studies described nonsurgical interventions and compared these interventions to another intervention (17 studies),[28,29,31,33,34,37,38,40-45,48,49,54,58,67] placebo (9 studies),[30,32,35,36,39,47,50,52,53] or usual care (4 studies)[46,64-66] Studies were conducted in 16 countries (United States, Canada, the United Kingdom, Australia, Finland, the Netherlands, Sweden, Czech Republic, Germany, Hungary, Poland, Ukraine, Turkey, India, Egypt, and Brazil). Of the 29 included studies, 4 studies were assessed as good quality,[35,47,52,53] 8 as fair quality,[30,38,39,42,45,49,50,54] and 17 as poor quality.[28,29,31-34,36,37,40,41,43,44,46,48,64-66]

LNG-IUS

LNG-IUS was an effective intervention for reduction of abnormal cyclic uterine bleeding in all seven of the identified studies.[28,41-46] Five studies that measured menstrual blood loss (MBL) directly from collected sanitary materials documented 70 to 87 percent reductions in bleeding when comparing treated women with their baseline.[28,41-43,45] When measured, 80 percent or more of women who were enrolled because they met criteria for heavy menses achieved normal total blood loss. These improvements were significantly greater than changes in comparison groups treated with NSAIDs, COCs, progestogens, and usual care. Evidence suggests the LNG-IUS effectively reduces self-reported symptom severity and duration of bleeding. A single study among women scheduled for hysterectomy found that LNG-IUS users were more likely to cancel their surgery compared with women in the usual care group.[46]

NSAIDs

In 13 studies, NSAIDs including mefenamic acid, naproxen, meclofenamate, and flurbiprofen given at the onset of menses for up to 5 days reduced MBL when compared with baseline.[28-40] NSAIDs are effective when compared with placebo.[35,39,68] Overall, 6 of 13 studies provided statistical comparisons to baseline only. Evidence is equivocal, one trial each, showing NSAIDs are similar in effectiveness or superior to oral norethisterone.[33,37] When measured, specific NSAIDs have been shown to reduce blood loss by 20 to 59 percent.[28-31,33-35,38-40,68] While NSAIDs can significantly reduce MBL, they did not consistently reduce bleeding to levels considered clinically normal (i.e., less than 80 ml) in all patients. There was considerable variability in response, with some patients experiencing an increase in blood loss during treatment. Studies evaluated treatment durations from one to six menstrual cycles. There were no differences in MBL reductions between NSAIDs and oral norethisterone or COCs. There were also no differences seen between individual types of NSAIDs, specifically mefenamic acid and naproxen. The most recent study found similar reductions in patient-reported assessments of bleeding severity when NSAIDs plus TXA was compared with TXA alone.[40]

TXA

All seven RCTs including TXA treatment demonstrated effectiveness for improving heavy bleeding.[29,34,40,47-50] TXA at a dose of 1.95 to 4.5 grams per day for 4 to 5 days from the onset of bleeding led to a clinically significant reduction in MBL, ranging from a 26 to 54 percent decrease in studies lasting up to a year. Both biologic and self-reported symptoms of bleeding severity were improved. In comparison to progestogens (norethisterone and medroxyprogesterone acetate), COCs, and NSAIDs, TXA provided greater reduction in MBL, however not all trials presented statistical analysis for head-to-head comparisons. No head-to-head comparisons of TXA versus LNG-IUS were identified.

COCs

Five RCTs included groups treated with COCs.[31,41,43,52,53] Measured reduction in bleeding was from 43 to 69 percent with complete normalization of total volume of bleeding achieved in 30 to 44 percent of women. One crossover comparison to mefenamic acid in 24 participants found both to be effective but lacked power to determine if either treatment was superior.[31] Two placebo-controlled studies found COCs effective for reducing menstrual bleeding and days of bleeding.[52,53] In the two head-to-head comparisons between COCs and LNG-IUS,[41,43] reductions in heavy menstrual bleeding were documented in both treatment groups. Women with a LNG-IUS had greater benefit.

Contraceptive Vaginal Ring

A single RCT compared the efficacy of the contraceptive vaginal ring with norethisterone in 95 women with abnormal cyclic uterine bleeding. The treatments were equally effective, reducing the patient-reported bleeding score by 67 percent in the contraceptive vaginal ring group and by 70 percent in the norethisterone group.[54]

Decision Aids

Three studies investigated decisions aids to assist women seeking treatment for heavy cyclic bleeding in making informed decisions about care.[64-66] Their findings suggest these tools do increase patient knowledge and enhance satisfaction with care. Overall, decision aids did not result in choices that influence disease symptoms in directly measurable ways. One study found fewer women who received the decision aid ultimately choose surgical referral and hysterectomy.[65] However this treatment choice cannot necessarily be linked to improvement in bleeding symptoms.

KQ 2. Harms of Interventions for Management of Abnormal Bleeding

Capturing useful information about potential harms of treatment for reproductive-age women that is specifically applicable to interventions for abnormal bleeding is a challenge because many agents have multiple indications and harms are often not well-studied in reproductive-age women. A wide range of interventions are used to treat abnormal bleeding. Twelve interventions relevant to the primary care setting were identified for this report. In this section we have restricted brief summaries to medications only (behavioral and lifestyle interventions, acupuncture, and decision support tools, each with little potential for serious harm, are discussed in the full report). We summarized harms and present findings in this order:

- Addressing the clinical trials included in this review.
- Compiling the key content of package inserts.
- Searching for surveillance studies that aimed to examine risk of harm in large populations of individuals (i.e., 1,600 or more) for specific interventions.
- Providing information from existing contemporary reviews and guidance on harms for common medications with broad indications.

We have grouped the interventions together, presenting those for abnormal irregular uterine bleeding first, followed by those for abnormal cyclic uterine bleeding. In instances in which the agent was used for both conditions the information is presented only once.

Metformin and Exenatide

In the included trials, metformin is associated with increased gastrointestinal (GI) symptoms including abdominal pain, nausea, and diarrhea.[55-57] This is compatible with the package insert.[69] Severe harms of metformin detected in larger studies, typically among older adults with type 2 diabetes, include lactic acidosis, serious hypoglycemia (most often in combination with other agents) and liver failure. Incidence of such serious harms is below 1 in 10,000 and may be as low as 1 per 100,000 person-years of exposure.[70]

Exenatide is typically used as a second agent when adequate glycemic control is not achieved with a single diabetes treatment. Its harm profile is uninformed by the literature in this review which included only one study with 40 women treated.[57] The package insert suggests hypoglycemia is the most serious side effect,[71] and large scale surveillance studies have not confirmed initial concerns that pancreatitis was more common among those treated.[72,73] Reviews including data about harms identify metformin as a first-line agent of choice for diabetes management, and concur that both agents are associated with excess GI complaints.[74-76]

Progesterone

Route of progestogen administration was compared in one comparative effectiveness trial for women with irregular menses.[59] In the remaining studies, progestogens were included as the comparator arms (in each case hypothesizing and documenting the superiority of the agent under study) or within COCs.[33,37,42,44,45,48,49] The progesterone-releasing intrauterine system is separately reviewed below.

Progestogens, like depot medroxyprogesterone acetate (DMPA), and vaginal micronized progesterone gel are associated with increased complaints of weight gain, fluid retention, abdominal pain, nausea, change of mood, and change in appetite. Many of these were documented in the included studies which were typically under-powered or made comparisons to other active agents, making comparisons of risk of side effects less informative. Among the most common complaints associated with progestogens is irregular bleeding. Package inserts also note potential dangers of exposure to high doses in pregnancy.[77]

A surveillance study has linked DMPA to increased future rate of fractures (though analyses were not controlled for key confounders like smoking and body mass index),[78] while another large study showed recovery of normal bone density within 2 to 3 years of ceasing use.[79] Some data suggest use of progestogens is associated with increased risk of deep venous thrombosis, though other research restricted to those using particular drugs for the indication of heavy menses demonstrates that women with heavy menses have higher risk of deep vein thrombosis regardless of the intervention they use suggesting some degree of confounding by the indication

for which the drug is given.[80] Reviews and meta-analyses confirm common side effects, including progestogens being a cause of irregular bleeding.[81]

COCs

Primary care providers and many women are aware of the most serious risks of COCs and the more common side-effects including edema, nausea, breast tenderness, skin changes, and GI symptoms. The studies in this review reported harms profiles for common symptoms similar to package insert documents.[82-85] Certain risks like that for venous thromboembolism, myocardial infarction, cerebral hemorrhage, hypertension, gallbladder disease, and benign liver tumors are also well documented. Patients and clinicians should be alerted to factors that increase risk of complications such as cigarette smoking, advancing age (with 35 often used as a threshold), and predisposition to thrombotic events. Two recent systematic reviews have reiterated increased risk for deep venous thrombosis with a suggestion that risk is lowest in those COCs containing levonorgestrel or norgestimate as the progestogens.[6,86]

Cabergoline

The sole study of cabergoline in this review was exploratory with 14 women with PCOS and 15 normal controls.[60] When used for treatment of prolactinoma, this drug is associated with nausea, headache, dizziness, lack of energy, and constipation. Cochrane reviews on three different conditions found no difference in overall risk of harms for cabergoline compared with placebo,[87,88] however a review of use for Parkinson's patients revealed increased valvular heart disease on echocardiogram with few symptomatic individuals.[89,90] The applicability of this data to young women with irregular menses is very limited.

LNG-IUS

Participants in the included trial of use of the LNG-IUS for abnormal cyclic uterine bleeding had few serious complications. Common side effects include changes in bleeding pattern including spotting and complete absence of menses. Abdominal pain/bloating, headache, depressed or altered mood, heavy bleeding, breast tenderness, and intrauterine device expulsion are expected to occur in approximately 5 percent or more of women using this treatment, as reflected in package inserts.[91,92] Surveillance studies provide good estimates from large registries of users. Difficult insertions occur in 3 to 4 percent of women, with painful insertion occurring in about 1 percent.[93,94] Risk of uterine perforation is between 0.9 and 2.6 per 1,000 users and the majority are not recognized at the time of insertion.[94-97] Nulliparous status and noncontraceptive indications do not appear to influence risk of perforation. Hair loss, that is known to be reversible in many but not all patients, occurs in about 1.8 per 1,000 users.[95] The LNG-IUS is not associated with increased risk of deep vein thrombosis in more than 8 million person-years of observation.[98-100] Systematic reviews match package insert and surveillance data also noting that expulsion occurs in 5 to 16 percent of women.[81,84,101,102]

Contraceptive Vaginal Ring

In the single trial of the contraceptive vaginal ring included in this review, the incidence of nausea, headache, and breast tenderness was comparable in both treatment groups during three cycles of treatment. The contraceptive vaginal ring users were less likely to report breakthrough bleeding than women taking norethisterone. Local events, including vaginal discomfort, vaginitis, foreign body sensation and coital problems were reported more frequently in ring-

users, but no one discontinued treatment due to adverse events. Product materials note that the contraceptive vaginal ring is contraindicated in cigarette smokers over age 35 due to increased risk of venous thromboembolism. A 15-year cohort study that included over 38,000 person-years of contraceptive vaginal ring use reported an elevated adjusted relative risk of 2.5 (95% CI, 1.4 to 4.4) for thrombotic stroke and 2.1 (95% CI, 0.7 to 6.5) for myocardial infarction compared with women (over 9 million person-years) who had not used hormonal contraception.[98] Systematic reviews have noted that the risk of venous thromboembolism for the contraceptive vaginal ring was elevated and similar to COCs.[103]

NSAIDs

NSAIDs are generally dosed intermittently in young women with problem bleeding. This makes detection of harms challenging. Complaints commonly reported in trials included: abdominal pain, nausea, gastritis, and light headedness or dizziness. Less common events included rashes and itching. These agents include a boxed warning on the product labels about cardiovascular and GI risks.[104-106] Upper gastrointestinal bleeding occurs in approximately 1 percent of patients treated for 3 to 6 months and at higher rates with longer use.[105-107] However, the majority of use assessed in this way is chronic, daily use. Product materials note that short term use is not without risk but do not provide risk estimates. Other common side effects include edema, abdominal pain, constipation, nausea, vomiting, heart burn, headache, nervousness, and conflicting central nervous system complaints like anxiety and tremor as well as malaise and somnolence. A pooled analysis of trials found mild neurologic and GI adverse events were more common in those treated than among placebo users.[108] The available reviews note additional investigation is required to clarify potential cardiovascular risks.[109,110]

TXA

Within studies in our review similar numbers of participants withdrew from TXA treatment arms as from placebo and comparison groups.[47,48] Side effect profiles were similar across those treated and untreated with the agent who remained in trials. The Food and Drug Administration has examined concerns about changes in QT-interval changes on electrocardiograms, but overall the number of subjects included in trials was considered to be low for evaluating harms and drug safety.[111] The updated prescription label now includes headache, nasal and sinus symptoms, back pain, and abdominal pain as occurring in more than 10 percent of those taking the drug.[112] Joint pain, muscle cramps and spasms, migraine, anemia, and fatigue occur in more than 5 percent of users. Post-marketing reports have identified thrombosis, allergic reactions including anaphylaxis, and visual disturbances.[112] This led to contraindications similar to those for COCs recommending that women with any history of thrombotic disease, risk for thrombotic disease, who smoke, are over age 35, or who concomitantly use tissue plasminogen activator, avoid the drug. Several reviews have examined harms and concluded that GI effects are most common and no thrombotic events were identified in 10 study populations.[113-116] It is important to note that overall these trials are small and large-scale surveillance data over time will likely be required for definitive answers.

Discussion

Summary of Strength of Evidence and Findings

The strength of evidence tables (Table B and Table C) summarize the total number of studies and within those studies the number of women who received the specific intervention. The tables also provide the assessment of the risk of bias, consistency of findings across trials, directness of the evidence that treatment improves the symptom, and precision of the estimates provided by the literature.

Overall the evidence to answer KQs about the management of AUB did not reach standards for high strength of evidence for any intervention from the literature relevant to treatment of women with irregular uterine bleeding (Table B). COCs, as represented in a single good quality placebo controlled trial with 201 participants, documented effectiveness.[51] The treatment effect was large with improvement in bleeding patterns reported for more than 80 percent of women taking COC compared with 45 percent for the placebo group. Combined, these factors provided moderate evidence of benefit. Use of metformin is supported by low strength of evidence predominantly related to small trials of somewhat limited quality. For the remainder of the interventions investigated for management of irregular uterine bleeding, there is insufficient evidence that follows from single and/or lower quality studies.

Table B. Strength of evidence for improving menstrual regularity (KQ1A)

Intervention Quality: Studies (Subjects Assigned to Intervention)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence[a]	Findings Comparisons
Progestogen[b] Poor: 1(69)[59]	High	NA	Direct	Imprecise	Insufficient	Not analyzed by arm
COC[c] Good: 1(101)[51]	Low	NA	Direct	Precise	Moderate	Cycle control improved:[d] 87% COC vs. PBO, p<0.001[51]
Metformin[e] Poor: 3(81)[56-58] Fair: 1(45)[55]	Medium	NA	Direct	Imprecise	Low	Delay to first ovulation:[f] 24 days MET vs. PBO, p=0.02[55]
Exenatide[g] Poor: 1(20)[57]	High	NA	Direct	Imprecise	Insufficient	Small, poor quality trial
Cabergoline[h] Good: 1(8)[60]	Low	NA	Direct	Imprecise	Insufficient	Cycle control improved:[i] 100% CBG vs. PBO, p=NR[60]
Diet[j] Poor: 1(24)[62]	High	NA	Direct	Imprecise	Insufficient	Not analyzed by arm

Table B. Strength of evidence for improving menstrual regularity (KQ1A) (continued)

Intervention Quality: Studies (Subjects Assigned to Intervention)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence[a]	Findings Comparisons
Exercise[k] Poor: 1(34)[61]	High	NA	Direct	Imprecise	Insufficient	Not analyzed by arm
Acupuncture[l] Poor: 1(33)[61] Fair: 1(23)[63]	High	NA	Direct	Imprecise	Insufficient	Menstrual regulation:[m] 86% MP-ACU > R-ACU, p<0.05[63]

CBG = cabergoline; COC = combined oral contraceptive; MET = metformin; MR-ACU = menstruation-promoting acupuncture; NR = not reported; PBO = placebo; R-ACU = routine acupuncture

[a]Overall strength of evidence assessment based on good and fair quality studies only.

[b]Oral dydrogesterone (n=35) vs. 8% vaginal micronized progesterone (n=34).

[c]Triphasic norgestimate-ethinyl estradiol vs. placebo (n=100).

[d]Subject assessment.

[e]Poor quality studies: metformin vs. N-acetyl cysteine (n=50), exenatide (n=20), or placebo (n=12); Fair quality study: metformin vs. placebo (n=47).

[f]Mean days to ovulation.

[g]Compared with metformin (n=20) or metformin plus exenatide (n=20).

[h]Compared with placebo (n=6).

[i]Menstrual cyclicity restoration in oligomenorrhea or spontaneous menses in amenorrhea.

[j]Low-fat diet (n=12) vs. low-carbohydrate diet (n=12).

[k]Compared with acupuncture (n=33) or no intervention (n=17).

[l]Poor quality study: acupuncture vs. exercise (n=34) or no intervention (n=17); Fair quality study: mind tranquilizing acupuncture vs. routine acupuncture (n=17).

[m]Patients cured or markedly relieved.

For management of heavy cyclic bleeding, the literature was more robust (Table C). COCs are supported by high strength of evidence for the purpose of decreasing MBL. The LNG-IUS, various NSAIDs, and TXA are also effective for reducing the amount of measured menstrual bleeding and are each supported by moderate strength of evidence. In head-to-head comparisons with statistically significant differences, the LNG-IUS has one trial showing superiority to NSAIDs,[28] two showing superiority to COCs,[41,43] and two showing superiority to progestogens.[42,44,45] COCs were equivalent in one trial compared with an NSAID.[31] TXA was also superior to NSAIDs,[29,34] and when combined with an NSAID was superior to TXA alone.[40] Most of these interventions have been shown to have additional positive effects, typically including shorter duration of bleeding and improvement in symptoms when participants used standardized scoring systems to report treatment response.

Table C. Strength of evidence for improving heavy menstrual bleeding (KQ1B)

Intervention Quality: Studies (Subjects Assigned to Intervention)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence[a]	Findings[b] Comparisons
LNG-IUS Poor: 5(173)[28,41,43,44,46] Fair: 2(104)[42,45]	Medium	Consistent	Direct	Precise	Moderate	71% and 94% reduction in MBL in 2 head-to-head studies LNG-IUS > MPA, p<0.001[42] LNG-IUS vs. NOR, p=NS[45]
NSAID Poor: 9(192)[28,29,31-34,36,37,40] Fair: 3(129)[30,38,39,68] Good: 1(32)[35]	Medium	Consistent	Direct	Imprecise	Moderate	28% to 49% reduction in MBL in 3 placebo controlled trials; 46% and 47% reduction in MBL in 1 head-to-head study (2 NSAID arms) MFA vs. PBO, p=NR[30] p<0.001[39,35] MFA vs. NPX, p=NS[38]
TXA Poor: 4(202)[29,34,40,48] Fair: 2(260)[49,50] Good: 1(123)[47]	Medium	Consistent	Direct	Precise	Moderate	26% and 40% reduction in MBL in 2 placebo controlled trials; 45% reduction in MBL in 1 head-to-head study TXA vs. PBO, p<0.001[50,47] TXA > NOR, p<0.001[49]
COC[c] Poor: 3(90)[31,41,43] Good: 2(269)[52,53]	Low	Consistent	Direct	Precise	High	64% and 69% reduction in MBL in 2 placebo controlled trials COC vs. PBO, p<0.001[52,53]
Progestogen[d] Poor: 1(50)[48] Fair: 4(173)[42,45,49,54]	Medium	Inconsistent	Direct	Imprecise	Insufficient	20% increase to 87% reduction in MBL in 4 head-to-head studies MPA < LNG-IUS, p<0.001[42] NOR < LNG-IUS, p=NS[45] NOR < TXA, p<0.0001[49] NOR vs. CVR, p=NS[54e]
CVR Fair: 1(48)[54]	Medium	NA	Direct	Imprecise	Insufficient	67% reduction in MBL[e] in 1 head-to-head study CVR vs. NOR, p=NS[54]

COC = combined oral contraceptive; CVR = contraceptive vaginal ring; LNG-IUS = levonorgestrel-releasing intrauterine system; MBL = menstrual blood loss; MCF = meclofenamate; MFA = mefenamic acid; MPA = medroxyprogesterone; NA = not applicable; NOR = norethisterone; NPX = naproxen; NR = not reported; NS = not significant; NSAID = nonsteroidal anti-inflammatory drug; PBO = placebo; TXA = tranexamic acid

[a]Overall strength of evidence assessment based on good and fair quality studies only.

[b]Change in menstrual blood loss from baseline measured by the alkaline hematin method (unless otherwise noted) from good and fair quality studies.

[c]Ethinyl estradiol and levonorgestrel (n=71) or norethindrone and ethinyl estradiol (n=19) or estradiol valerate and dienogest (n=269).

[d]Medroxyprogesterone (n=177) or oral norethisterone (n=113) or depot medroxyprogesterone (n=44).

[e]Percent change in menstrual blood loss measured by the pictorial blood loss assessment chart.

Applicability

Applicability describes the extent to which results observed in published studies from this review are likely to reflect the expected outcomes when an intervention is applied to broader populations in real-world conditions. Studies for this review were intended to provide information to inform primary care management of irregular or cyclic AUB. In shaping the methods for this review, we engineered the report so that the included research is applicable to primary care of women with these complaints in the United States. Because we narrowed our focus to symptomatic women of reproductive age with chronic complaints of abnormal bleeding, this comes at the cost of fewer studies being addressed. However, it assures that studies included were explicitly designed to examine the effectiveness of the treatments for improving the outcomes of interest in the populations of interest. Applicability of the findings is therefore high.

For each intervention, it is important to note the following provisions. The results of this review apply for women:

- Who are reproductive age and state they have an irregular pattern of menstrual bleeding or heavy cyclic menstrual bleeding;
- Without abnormal findings on pelvic exam or on ultrasound report (fibroids, polyps);
- Without an intrauterine device in place, and who are not pregnant or lactating;
- Who are healthy, and without renal impairment, hepatic impairment, intestinal disease, thyroid disease, abnormal cervical cytology, noncyclic bleeding, history or presence of significant medical problems (e.g., thromboembolic disease, coagulopathy, subarachnoid hemorrhage, endocrine disorders, or eye disease);
- For whom any additional clinically determined diagnostic and screening tests have been completed to rule out other causes of abnormal bleeding;
- Does not have any of the contraindications found in the Food and Drug Administration sources discussed in the main document and do not have risks of drug-drug interactions if they take multiple prescription medications.

This review was not designed to guide evaluation of women with abnormal bleeding, rather to address what treatments have evidence of effectiveness once the diagnosis is established and primary care management is to be initiated.

Overall applicability was high. However, often women who are in trials do not reflect the full range of those with abnormal bleeding seen in primary care. Study participants were more likely to be normal weight, nonsmokers, with few, if any concomitant conditions. The interventions (except in the case of specific comparators as noted) are available in the same doses and formulation in the United States. Outcomes such as measured blood loss, self-reported symptom severity and days of bleeding are of direct relevance to women with abnormal bleeding. Our findings are sparse for outcomes which can be considered essential for a condition like AUB that is defined by symptoms. Important outcomes include satisfaction with response to treatment, definitive assessments of whether or not the women considered their complaint resolved, and whether they wished to continue the same treatment or add additional treatments. Followup in general was brief, so the findings may not apply well to management of a chronic condition like abnormal bleeding. This makes assessments of harms challenging since use of interventions over extended periods may have different risk profiles from short timeframes like one to six cycles.

Research Gaps

Recent improvements in unifying nomenclature and formalizing consensus definitions for the clinical groupings of bleeding abnormalities[9] will likely continue to have a positive influence on the ability to properly interpret the findings of individual studies, to identify groups of studies with comparable methods, and to aggregate results. An array of methodologic recommendations and specific research needs are detailed in the full report. Common themes included the need for larger, better controlled RCTs, with combinations of biological and patient-reported outcomes and that evaluate outcomes over longer periods of time, at least past 1 year. Populations need to become more representative of those seeking care (teens, heavier women, those with common comorbidities like diabetes) and need to directly address common clinical interventions like COCs and progestogens that are represented in the literature by a surprisingly small number of older studies, given how ubiquitous their application is in clinical care. No studies examine trajectories through care, mapping sequential treatment options or costs of care based on the initial treatment strategy assigned. No studies examined combining effective treatments, especially in women who had improvements but did not reach satisfactory control of bleeding or cycle regularity. Overall trial designs should begin to shift towards effectiveness from efficacy, moving beyond the level of proof of concept that is required for drug and device approval to a deeper level that can better inform care, cost considerations and policy.

Conclusions

Women who have problematic irregular or heavy cyclic menstrual bleeding have a number of treatment options available that are supported by systematic review of the research literature. These include high strength of evidence that COCs can improve menstrual regularity for women with irregular bleeding patterns. Metformin is supported by moderate strength of evidence for improving cycle regularity especially among women with PCOS. This provides both a contraceptive and a noncontraceptive option for irregular menses. Other interventions like progestogens are associated with statistically and clinically meaningful improvements from baseline patterns, however the overall evidence is insufficient from well-designed, larger studies with ability to directly compare treatment arms rather than only pre-post measures within groups.

Multiple interventions for heavy cyclic bleeding are supported by evidence that they reduce MBL. These include strong evidence that COCs are effective and moderate strength of evidence that the LNG-IUS, NSAIDs, and TXA reduce bleeding relative to baseline, decrease total volume of bleeding when comparisons are made across treatment groups, and when measured, decrease days of bleeding per cycle. In direct comparisons, LNG-IUS is superior to NSAIDs. TXA is superior to NSAIDs and TXA combined with an NSAID was superior to TXA alone. Results from COC and NSAID comparisons suggest comparable effectiveness. Not all women will benefit from these interventions. Across agents data are sparse to evaluate long-term improvements and risk of harms.

Limitations include a predominance of small, short trials lacking standard terminology and diagnostic criteria for identifying and including women with AUB. Tools for collecting outcome data are crude (collection of sanitary products) and may contribute to a high rate of attrition. Biologic outcomes, like measured blood loss and hemoglobin or hematocrit levels, may neglect the importance of patient-reported outcomes that assess whether symptoms are considered resolved by women themselves. Nevertheless, the variety of effective options suggests many women can achieve symptom relief and have available choices that address both symptoms and

contraceptive or fertility desires, as well as potentially improving other symptoms like menstrual cramping.

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Introduction

Background

Condition

Abnormal uterine bleeding (AUB) is among the most common of gynecologic complaints from reproductive-age women in ambulatory care settings—of similar frequency to the number seeking care for urinary tract infections and vaginitis. In the general population, AUB is estimated to affect 11 to 13 percent of reproductive-age women. The prevalence of AUB increases with age, reaching 24 percent in women aged 36 to 40.[1,2] In addition to gynecologists, all primary care practitioners including pediatricians, family physicians, advanced practice nurses, and internists, will encounter the need to evaluate, treat, or refer women with bleeding-related symptoms.[3] Women generally present because the amount, timing, or other characteristics of the bleeding have changed from their individual norm.

Population norms for menstrual bleeding, as established by 5th and 95th percentiles, are:[4-7]

- Frequency of menses within a 24 to 38 day window
- Regularity (cycle-to-cycle variation) within 2 to 20 days
- Duration of flow from 4 to 8 days
- Volume of blood loss from 5 to 80 ml

Symptoms outside this range or different from normal for the individual can become problematic and deserve evaluation because they can warn of underlying conditions. Common problems include worry about the cause, embarrassment if the bleeding includes flooding-type bleeding with saturation of clothing, missed work and responsibilities, limitations of social activities and exercise, decreases or changes in sexual activity, and frustration with costs of sanitary protection.[1,8] Collectively, the effects of troublesome bleeding reduce quality of life and drive desire for information about causes and treatment options.[1,8]

There is not a clear consensus on the clinical evaluation of a patient presenting with abnormal bleeding. Recommendations suggest that initial evaluation confirm the source and timing of bleeding, and exclude certain architectural etiologies, cancer, coagulation defects, and systemic disease. The 2011 International Federation of Gynecology and Obstetrics (FIGO) classification recommends a structured history followed by uterine evaluation.[9] In the research setting, the alkaline hematin method is the preferred technique for direct measurement of total menstrual blood loss (MBL). The pictorial blood loss assessment chart is a semi-quantitative tool for uniform reporting of bleeding as represented by the degree of saturation of sanitary pads and tampons. Diagnostic tools and evaluation strategies are not within the scope of this review;[10,11] however, the review captures the operational definitions used by researchers and addresses applicability of the findings to contemporary practice.

Terminology

Nomenclature to classify symptomatic problem bleeding has evolved steadily over the past several decades.[12] Early classifications primarily used characteristics of the bleeding to group women. Terms like menorrhagia (abnormally long or heavy menses) and metrorrhagia (bleeding at irregular intervals) were often linked with timing (short or long intervals) and amount (heavy or light) to infer whether or not regular and predictable ovulation was occurring and further assign likely ovulatory or anovulatory status. These terms are generally applied without formal

documentation of ovulatory status. Furthermore, previously applied terms like "dysfunctional uterine bleeding" also carried a variable element of recognition that the label was a diagnosis of exclusion.[12] The resulting challenge was that practitioners and researchers applied different exclusions before selecting interventions or enrolling patients. Over time, differences in terminology choice and in operational definitions have resulted in wide inconsistencies in application of diagnostic terms.[4,12-14]

Recent international consensus recommendations, formally adopted by FIGO in 2010 and published in 2011, more consistently align terminology by creating two major groupings (i.e., discrete structural vs. nonstructural) for causes of bleeding.[9,15,16] The FIGO classification includes nine categories of abnormal bleeding arranged according to the acronym PALM-COEIN:[9,16] four have objective visual criteria detected by imaging, biopsy, or pathology (i.e., PALM: **p**olyps; **a**denomyosis; **l**eiomyomata; and **m**alignancy and hyperplasia) while another five are not directly related to structural abnormalities (i.e., COEIN: **c**oagulopathy; **o**vulatory dysfunction; **e**ndometrial; **i**atrogenic; and **n**ot yet classified).

If we map the intended focus of this comparative effectiveness review (CER) to the FIGO classification, we are addressing the COEIN groups that are characterized as "ovulatory dysfunction" (AUB-O), "endometrial hemostatic dysfunction" (AUB-E), and "not yet classified" (AUB-N) abnormal bleeding. However it is crucial to note that direct measures of ovulation are not employed in most available literature and endometrial samples for classification are even more rare, except when used to rule out malignancy. Indeed much remains to be explained about the pathophysiology of the very common and problematic complaint of unpredictable and/or heavy bleeding. In summary, the relevant population for this review includes nonpregnant women from menarche to menopause who have had abnormal bleeding (scant or heavy) for 3 months or longer that is not attributed to structural abnormalities, coagulation defects, systemic illnesses, or medications.

While some reviews further subdivide women experiencing AUB into age groups,[17] such as those near menarche and in the perimenopausal timeframe, we plan to retain an emphasis on categorization. Women across the reproductive lifespan can have abnormal bleeding that arises from ovulatory dysfunction or endometrial processes.[18] While the underlying causes may vary, for instance from lack of consistent regulation of the hypothalamic-pituitary-ovarian axis in teens near the onset of menses, and from lack of ovarian reserve in perimenopausal women, the treatment options overlap.[3] We will report when research was done with an age-restricted population but will otherwise cover all the relevant literature regardless of reproductive age or reproductive history of participants.

Therapies

Current guidelines from professional societies including the American Congress of Obstetricians and Gynecologists,[19-22] the American Academy of Family Physicians,[23] and the National Institute for Clinical Excellence[24] recommend medical therapy, including the levonorgestrel-releasing intrauterine system (LNG-IUS), nonsteroidal anti-inflammatory drugs (NSAIDs), antifibrinolytics, combined oral contraceptives (COCs), and progestogens, as the first-line treatment for irregular uterine bleeding and abnormal cyclic bleeding.

In a recently published research article,[25] Matteson and colleagues examined the practice patterns and attitudes from a U.S. sample of obstetricians and gynecologists regarding the medical treatment of women with AUB. The authors reported that practicing obstetrician-gynecologists most frequently selected COCs for the treatment of both irregular and abnormal

cyclic menstrual bleeding and that participants lacked an overall awareness of current evidence on effectiveness of common treatment options for AUB.[25] However, another recent publication[26] reported that, that in conflict with recommendations, uterine-preserving surgical procedures were the most common first-line treatment for women with heavy menstrual bleeding within a large cohort from a national claims database of large employers.

Primary Care Treatment Options

Pharmacologic therapies to treat AUB in the ambulatory setting include estrogens, progestogens, combination (estrogen and progestogen) hormonal formulations, NSAIDs, antifibrinolytics, and progesterone-releasing intrauterine devices (IUDs). Medical interventions are generally considered first-line treatment.[27,28] Surgical intervention is usually reserved for women with persistent bleeding that does not respond to medical therapy or for women who have finished childbearing and do not wish to continue medical therapy indefinitely.[2,23]

LNG-IUS

A pooled analysis of data from five randomized controlled trials (RCTs) reported that the LNG-IUS provided clinically and statistically significant sustained reductions in MBL.[29] Locally released progesterone from the IUD reduces growth of the uterine lining, minimizing the tissue available to be shed during menstruation. IUDs are used as contraception by approximately 5 percent of women in the United States.[30] Based on large-scale claims data, use of the LNG-IUS increased 19-fold between 2002 and 2008 to 7.7 per 1000 women, becoming the most commonly used IUD in the United States.[31]

NSAIDs

NSAIDs are commonly used to treat AUB (more recently termed AUB-E) because of the role of prostaglandins in the pathogenesis of heavy menstrual bleeding. Higher levels of prostaglandin E2 have been observed in the endometria of women with heavy menstrual bleeding.[32] Additional evidence points to an abnormal ratio of specific prostaglandins as a contributing factor to problems with hemostasis.[32] NSAIDs act to reduce prostaglandin synthesis by inhibiting the enzyme cyclo-oxygenase and therefore reducing endometrial prostaglandin levels leading to decreased potential for vasodilation and angiogenesis.[33] Based on a limited number of small studies, a 2007 Cochrane Review[34] found that NSAIDs were superior to placebo but less effective than tranexamic acid and LNG-IUS at reducing MBL.

TXA

TXA is an antifibrinolytic that slows the breakdown of fibrin in blood clots. By decreasing the degradation of physiologic blood clots, blood flow from uterine vessels sealed by the clot is decreased. Since it is not a hormonal agent and does not have contraceptive effects it may be useful for women who desire a pregnancy or for whom hormonal treatment is contraindicated. TXA appears to be well-tolerated and cost-effective, reducing blood loss considerably and improving health related quality of life for women with menorrhagia.[35]

COCs

COCs are commonly used to manage abnormal bleeding associated with ovulation since they work in part by superimposing an organized cycle and discourage thick growth of the uterine lining. The American Congress of Obstetrics and Gynecologists 2010 Practice Bulletin for

noncontraceptive uses of hormonal contraceptives recommends COCs as a reasonable choice to regulate and reduce menstrual bleeding, based on good and consistent scientific evidence.[21] However, according to a 2009 Cochrane systematic review,[36] there is insufficient evidence to establish the effectiveness of the oral contraceptive pill compared with other medical therapies, placebo, or no therapy for the treatment of heavy menstrual bleeding.[36] In a clinical review for diagnosis and management of AUB,[37] authors assert that COCs are likely beneficial for treatment of anovulatory (i.e., acyclic) AUB but there is lack of good quality data to support their use in abnormal cyclic bleeding.[37] The COC is also known to cause abnormal bleeding patterns, with breakthrough bleeding reported as one of the most common reasons for discontinuation of COC use.[38] Additional data are needed on the number needed to treat and the number needed to harm for adverse effects.

Progestogens

During a normal cycle, the natural rise and fall of progesterone, which is produced by the ovary after ovulation, has multiple biological effects on the endometrium. These include "organization" that results in the coordinated withdrawal bleeding observed as the menses after progesterone levels fall. Cyclic administration of progestogens in women with AUB is intended to mimic natural production of progesterone in the luteal phase and then withdrawal, by providing the agent for a number of days, typically 10 to 14, after which bleeding occurs. Other methods of administration of progestogen, such as by long acting injection or oral contraceptive pills that contain only a progestogen, exploit a different biologic property of progestogens. When continuously administered, progestogens encourage endometrial quiescence and reduce growth of the endometrium. In women with AUB, these effects can modulate problematic symptoms by fostering endometrial stability and a relatively thin endometrium resulting in less bleeding. The American Congress of Obstetrics and Gynecologists practice bulletins on management of anovulatory bleeding and noncontraceptive uses of hormonal contraceptives note that progestogens are an appropriate first-line choice for medical management of irregular bleeding that results from lack of regular, predictable ovulation.[19,21]

Behavioral and Lifestyle Interventions

Diet and physical activity interventions have been proposed for irregular menstrual bleeding because irregular menses often indicate irregular or absent ovulation. Obesity and metabolic syndrome, including polycystic ovarian syndrome (PCOS), are associated with increased risk of anovulatory cycles. Trials that have achieved modest weight loss in infertile patients have restored regular ovulatory function in a majority of women with obesity-related subfertility.[39] Both aerobic and strength training as well as weight loss may improve blood sugar profiles and reduce relative or frank insulin resistance, which are intermediates to restoring regular menses in some women.

Complementary and Alternative Medicine

Initial literature scans suggested that there is an extremely limited body of literature on trials of complementary and alternative medicine for AUB. Complementary and alternative medicine based therapies are included as interventions of interest due to their increasing popularity among patients and growing interest to clinicians.[40]

Scope and Key Questions

Scope of the Review

The relevant population for this review includes nonpregnant women from menarche to menopause who have had AUB for 3 months or longer, that is not attributed to structural abnormalities, coagulation defects, systemic illnesses, or medications.

The literature reflects various management options for women with AUB with conflicting recommendations/summaries. Interventions of interest for this review include medical, complementary and alternative medicine, and behavioral/lifestyle interventions. This review does not consider surgical interventions for AUB, as surgical management is adequately covered by other groups conducting systematic reviews.

This review is focused on the evidence available to inform selection of nonsurgical options to treat AUB with an emphasis on interventions that are accessible to and within the scope of usual practice for primary care practitioners in a clinical care setting. This means that while we *did not* restrict literature review to studies conducted only in primary care settings, we did restrict the review to include only those interventions that could be deployed in primary care. We address abnormal bleeding that is chronic in nature, meaning the symptom has persisted for the majority of the prior 3 months, and is of two primary and common types: (1) irregular in timing (i.e., acyclic); and (2) abnormal though cyclic. We explicitly defined eligibility criteria using a PICOTS (population, intervention, comparator(s), outcome, timing, and setting) structure (Table 1).

Table 1. PICOTS

PICOTS Element	Description
Population:	Nonpregnant women from menarche to menopause who have had abnormal bleeding for 3 months or longer whose bleeding is not caused by structural abnormalities, coagulation defects, systemic disease, cancer, or medication. Two specific subtypes of abnormal bleeding will be the focus: • *Irregular uterine bleeding:* problem bleeding (frequent or infrequent) of 3 months or greater duration, excluding regular cyclic/menstrual patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, coagulation defects, and related systemic disease. • *Abnormal cyclic uterine bleeding*: problem bleeding of 3 months or greater duration, excluding irregular and unpredictable patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, coagulation defects, and related systemic disease.

Interventions:[a]	• Medical therapies
	  o Nonsteroidal anti-inflammatory drugs
	  o Antifibrinolytics
	  o Oral hormone treatments (e.g., oral contraceptives, progestogens)
	  o Levonorgestrel-releasing intrauterine system
	  o Vaginal ring contraceptive device
	• Behavioral strategies (e.g., stress reduction, weight reduction, exercise)
	• Complementary and alternative medicine therapies (e.g., acupuncture, herbal medicine)

Comparator:	Direct comparison among interventions listed above or comparison to placebo.

Table 1. PICOTS (continued)

PICOTS Element	Description
Outcomes:	• Bleeding profile (e.g., amount, frequency, duration, pattern, symptom bother, hematocrit) • Quality of life including both general and bleeding specific measures • Pain related to bleeding • Sexual function as reported by sexual function measures, general measures of sexual activity, frequency and satisfaction • Patient satisfaction with outcomes and acceptability of treatment • Fertility • Time to conception • Additional interventions including concurrent and consecutive surgical and nonsurgical treatments • Harms[b] (e.g., thromboembolic events, emotional side effects, weight gain, short- and long-term harms)
Timing:	Interventions initiated after symptoms present most months for 3 months or longer.
Setting:	Any clinical care setting.

PICOTS = population, intervention, comparator, outcome, timing, and setting
[a]Excluding surgical interventions and procedures such as endometrial ablation.
[b]Includes treatment-related adverse events (e.g., drug side effects); does not include consequences related to the failure to adequately treat the symptom.

Key Questions

Key Question 1A (KQ1A)

What is the evidence for the effectiveness of medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) for improving short and long-term outcomes in women with irregular uterine bleeding?

Key Question 1B (KQ1B)

What is the evidence for the effectiveness of medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) for improving short and long-term outcomes in women with abnormal cyclic uterine bleeding?

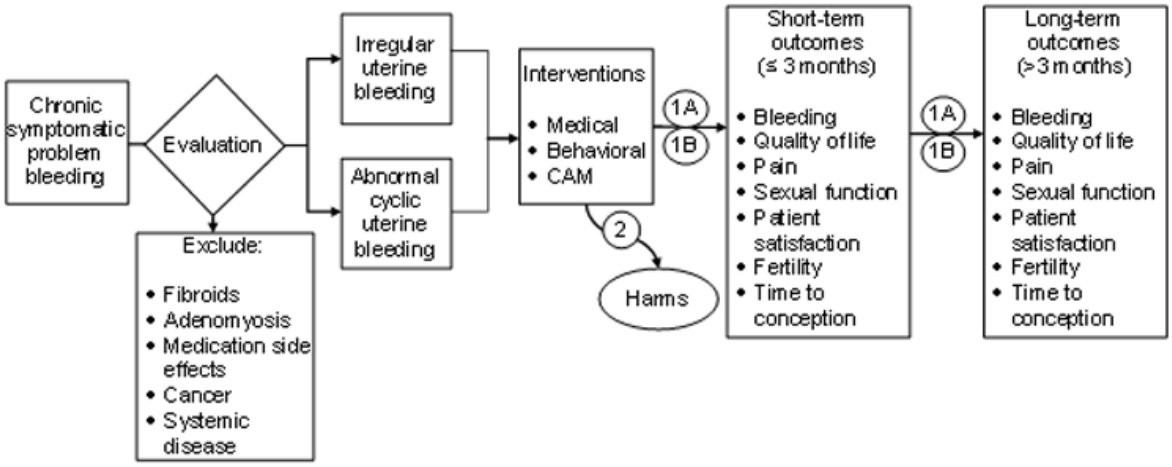
Key Question 2 (KQ2)

What are the harms, including adverse events, associated with medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) in women with irregular uterine bleeding or abnormal cyclic uterine bleeding?

Analytic Framework

We developed the analytic framework (Figure 1) drawn from clinical expertise of Key Informants and refined it with input from a Technical Expert Panel (TEP). The analytic framework illustrates the population, interventions, outcomes, and adverse effects that guided the literature search, study eligibility, screening, and synthesis.

Figure 1. Analytic framework



CAM = complementary and alternative medicine
Note: Numbers in circles represent Key Questions.

Organization of This Report

The Methods chapter describes our processes including our search strategies, inclusion and exclusion criteria, approach to review of abstract and full publications, methods for extraction of data into evidence tables, and compiling evidence. We also describe our approach to grading the quality of the literature and assessing the strength of the evidence.

The Results Chapter presents the findings of the literature search and review of the evidence by Key Question (KQ). When there are distinct populations in which the interventions have been studied such as enrollment based on differing criteria, we discuss related data together. Within KQs we present summary information in the order: devices, medications, lifestyle and behavior interventions, and complementary and alternative medicine. Within a category such as medication, we organize the results from greater number of studies to fewer, and presented the results of placebo controlled trials before direct comparisons.

The final section discusses the results and enlarges on the methodologic considerations relevant to each KQ. We also outline the current state of the literature and needs for future research on management of AUB. We include a list of abbreviations and acronyms at the end of the report followed by appendixes to provide further detail on our methods and the studies assessed. The appendices are as follows:

- Appendix A Literature Search Strategies
- Appendix B Abstract Review Form (KQ1)
- Appendix C Abstract Review Form (KQ2)
- Appendix D Full-Text Review Form (KQ1)
- Appendix E Full-Text Review Form (KQ2)
- Appendix F Cochrane Risk of Bias Tool
- Appendix G Cochrane Risk of Bias Criteria
- Appendix H Thresholds for Quality Assessment
- Appendix I Risk of Bias and Quality Score for Individual Studies
- Appendix J Evidence Table
- Appendix K Reasons for Exclusion (KQ1)

Methods

The methods for this comparative effectiveness review (CER) follow those suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[41] The main sections in this chapter reflect the elements of the protocol established for the CER; certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[42]

Topic Refinement and Review Protocol

The topic for this report was nominated by a health care professional using the Effective Health Care Web site (http://effectivehealthcare.ahrq.gov/). Working from the nomination, we drafted the initial Key Questions (KQs) and analytic framework and sought input from Key Informants representing family medicine, generalist and subspecialty obstetrics and gynecology, and midwifery. Key Informants uniformly stressed the importance of terminology and of establishing clear and distinct categories of women for whom the review is intended to apply and suggested framing the review from the vantage point of a primary care provider or specialist who is at the earliest stage of management of abnormal uterine bleeding (AUB), which is typically nonsurgical management. KQs were refined to reflect the feedback from Key Informants and address gaps in existing evidence reviews and knowledge base about management of AUB.

After review from AHRQ, the KQs and analytic framework were posted online for public comment. We received no comments during the public posting phase. We prepared final KQs and resubmitted them to AHRQ for review. We identified Technical Experts on the topic to provide assistance during the project. The Technical Expert Panel (TEP) included individuals with expertise in bleeding abnormalities, nomenclature and classification of AUB, and lead authors of ongoing reviews of surgical interventions. The TEP included five members serving as technical or clinical experts. To ensure robust, scientifically relevant work, we called on the TEP to review and provide comments as our work progressed. TEP members participated in conference calls and discussions through e-mail to:

- Refine the analytic framework and KQs;
- Discuss the preliminary assessment of the literature, including inclusion/exclusion criteria;
- Provide input on the information and domains included in evidence tables;

Literature Search Strategy

Search Strategy

Databases

We searched the following databases: MEDLINE® (PubMed interface), the Cumulative Index of Nursing and Allied Health Literature (CINAHL®), and Embase. All search results were limited to English language. Searches were further restricted from 1980 forward in order to ensure literature was relevant to current secular trends in practice as well as available treatment strategies. We carried out hand searches of the reference lists of recent systematic reviews related to management of AUB and the reference lists of included publications. Searches were executed between September 2011 and June 2012.

Search Terms

Each search strategy used a combination of subject headings (i.e., controlled vocabulary) and keywords appropriate for each database (Appendix A). The search strategies included terms related to AUB, along with drug and therapy terms relevant to the topic and focus of Key Question 1A (KQ1A) and Key Question 1B (KQ1B). For Key Question 2 (KQ2), we conducted a second, separate search in MEDLINE (PubMed interface), using controlled vocabulary and keywords focusing on adverse effects and harms associated with those drugs and treatments from our KQ1A and KQ1B included studies. We also employed a combination of subject headings and keywords to narrow retrieval to desired study types; for KQ1A and KQ1B, this included terms related to randomized controlled trials (RCTs), and for KQ2, terms geared toward also retrieving cohort and postmarketing surveillance studies.

Supplementary Information for KQ2

To further assess KQ2, we searched Internet resources to identify current research and regulatory information related to adverse effects and harms specific to those drugs and therapies from KQ1A and KQ1B included publications, with the term harm referring to any negative psychological, physical, or health system consequence associated with the intervention being studied. These searches were executed between January and March 2012. The Scientific Resource Center invited manufacturers of drugs from our included studies to provide Scientific Information Packets.

For each included intervention, we conducted searches of the Food and Drug Administration (FDA) database of approved drugs (Drugs@FDA) and DailyMed to locate the most recent label information, determine the approval date, ascertain therapeutically equivalent drugs, and find other relevant information related to harms. For those drugs no longer marketed or unavailable in the United States, label information (including indications and usage, and harms) was also retrieved from the regulatory agencies of other countries where the drug is approved (e.g., HealthCanada's Drug Product Database), drug information databases (e.g., Micromedex® and LexiComp®), and manufacturer or pharmaceutical company Web sites. Additionally, we searched the FDA's safety information and adverse reporting Web site (MedWatch) to verify the most recent changes to label information were included in our harms data.

To supplement the harms data extracted from package inserts and relevant studies, we adapted our primary PubMed search strategy to identify systematic reviews and meta analyses examining the therapeutic agents identified in our analysis of the literature for KQ1, limiting to items published since 2005.

To ascertain current and ongoing research, we searched clinicaltrials.gov with topic keywords (e.g., “abnormal uterine bleeding”, “menorrhagia”, “heavy menstrual bleeding”), looked at both recruiting and completed studies, and again focused on those drugs and therapies from KQ1A and KQ1B included publications.

Inclusion and Exclusion Criteria

To be considered for inclusion, studies had to explicitly define and describe the study population, the interventions, and outcomes.

For this CER, the population of interest included women with symptomatic cyclic or irregular uterine bleeding (Table 2). We excluded studies of women with AUB caused by coagulation defects, systemic disease (e.g., thyroid disease), structural abnormalities (e.g.,

fibroids, polyps), cancer, or medication side effects. Studies that included patients with AUB of mixed or ill-defined etiologies were reviewed for evaluable data from patients meeting the description of the population of interest. For KQ1A we included studies of women with polycystic ovarian syndrome (PCOS) if the patient baseline and outcome data included information on cycle regularity. We excluded studies of women with infertility if the primary treatment goal was conception.

Table 2. Definitions of eligible patient populations

Patient group	Description
Irregular uterine bleeding	Problem bleeding (frequent or infrequent) of 3 months or greater duration, excluding regular cyclic/menstrual patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, coagulation defects, and related systemic disease.
Abnormal cyclic uterine bleeding	Problem bleeding of 3 months or greater duration, excluding irregular and unpredictable patterns of bleeding, fibroids, polyps, adenomyosis, cancers, medication side effects, coagulation defects, and related systemic disease.

To be considered for inclusion, clinical research studies had to evaluate a nonsurgical intervention. For KQ1 and KQ2 we included data from controlled clinical trials (e.g., RCTs) designed to evaluate an intervention or treatment strategy for individuals from the population of interest. For KQ2, we also included data from uncontrolled observational studies, namely high-quality, large cohort studies, postmarketing surveillance studies, and registries/databases, with a population of 1,600 or more patients or records to capture information on adverse events or other harms.[43] We determined that a minimum sample size of 1,600 was needed in order to reliably detect harms with an estimated prevalence of 1 percent. We did not specify a minimal population size for KQ1. Several factors, including varying prevalence of cyclic and irregular patterns of bleeding and the large number of interventions under consideration for this review, make it difficult to reliably establish a minimum sample size for evaluating treatment effectiveness.

To balance resources and focus on literature of most immediate relevance to primary care practice in the United States, we excluded papers that were not published in English.[44]

Study Selection

We developed individual abstract and full-text screening forms for KQ1 and KQ2 (Appendixes B, C, D and E). We revised the forms following testing by the team. The forms were adapted for use in the Web-based systematic review product, DistillerSR (Evidence Partners, Ottawa, Canada).

We conducted screening in two phases: abstract and full-text screening. Publications were promoted to full-text review when one reviewer indicated that the publication met all inclusion criteria or when the title and abstract did not provide adequate information to make a determination. Two reviewers independently reviewed each publication at the full-text screening phase. Discordant classifications were resolved in team meetings including senior investigators.

Quality (Risk of Bias) Assessment of Individual Studies

Two senior team members independently assessed quality of the included studies; disagreements were resolved through discussion or third party adjudication as needed. We recorded quality assessments in tables, summarizing each study.

We used the Methods Guide for Effectiveness and Comparative Effectiveness Reviews[41] and the Cochrane Risk of Bias Tool[45] (Appendix F), an existing tool with established validity and

reliability, to assess methodological quality of included studies. This tool includes criteria for judging risk of bias for specific elements from five fundamental domains: sequence generation, allocation concealment, blinding, outcome data, and selective reporting (Appendix G) in RCTs. From these domains an overall assessment of risk of bias was calculated based on prespecified thresholds for modified quality assessment criteria from the Cochrane Risk of Bias (RoB) Tool (Appendix H). The overall risk of bias assessment was then expressed as one of three final study quality ratings: studies assessed as having a high risk of bias were categorized as "poor" quality studies; studies having a medium risk of bias were categorized as "fair" quality studies; and studies assessed as low risk of bias were categorized as "good" quality studies.

We assessed quality for the included studies that addressed KQ1 only. For KQ2, we sought evidence from varied sources; it was not possible to systematically assess the quality of the evidence related to harms. A summary of all component items and overall risk of bias/quality score for each included study is provided in Appendix I.

Data Extraction

We created uniform evidence tables to extract data and facilitate data synthesis. We collected those data related to population characteristics, type of abnormal bleeding, intervention characteristics, and outcomes including harms.

We evaluated the ability to capture data across publications about candidate effect modifiers and confounders of treatment response and uniformly extracted information about candidates including age, body mass index, parity, and smoking status. When available we also collected current and prior contraception, perimenopausal status, fibroid status, and comorbidities including diabetes and PCOS. The final evidence tables are provided in Appendix J.

Data Synthesis

A meta-analysis was not feasible for this review. Few studies had comparable treatment doses, interval, length of treatment, or duration of followup. Among those that did, the ability to aggregate data was limited by differences in outcomes measures which included measures of blood loss from sanitary product collection, and self-report using scoring systems including standardized pictorial systems.

For regularity of bleeding no two measures of outcome were the same. We provide a narrative synthesis of the available data from original research studies of acceptable quality for nonsurgical treatment of AUB.[46] We group findings and summary tables by KQ, intervention, and outcomes.

Strength of the Body of Evidence

The strength of evidence evaluation is stipulated in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[41,47] The guide emphasizes the following four major domains: risk of bias (low, medium, high); consistency (inconsistency not present, inconsistency present, unknown or not applicable); directness (direct, indirect); and precision (precise, imprecise) of the evidence. Risk of bias was derived from the quality assessment of the individual studies that addressed the KQ and specific outcomes under consideration.

We used explicit criteria for rating the overall strength of the evidence on each intervention into qualitative categories (e.g., low, moderate, high, and insufficient). We used established concepts of the quantity of evidence (e.g., numbers of studies, aggregate ending-sample sizes),

the quality of evidence (i.e., from the quality ratings on individual articles), directness of the outcomes for informing the KQs, and the coherence or consistency of findings across similar and dissimilar studies and in comparison to known or theoretically sound ideas of clinical or behavioral knowledge. For this CER, overall strength of evidence for each intervention was made based upon a qualitative consideration of the assessment for each domain.

We assessed the overall strength of evidence rating based on the assessments for the individual domains for cycle regularity (KQ1A) and menstrual blood loss (MBL) reduction KQ1B. Data from studies that were considered to be fair or good quality were included in the assessments. Poor quality studies were identified but not included in the assessment of strength of evidence. For KQ2, we did not rate of strength of evidence because a fully inclusive assessment of harms could not be completed for each of the 12 interventions that have been widely studied in populations that lack direct applicability to this report.

The overall strength of evidence was graded as "high", "moderate", "low", or "insufficient" (Table 3).[47] When no studies were available for an outcome or comparison of interest, or if the available evidence was weak (i.e. from studies with high risk of bias) we graded the evidence as insufficient.

Two senior investigators independently graded the body of evidence and final assignment was reviewed with the project team. We achieved alignment through group discussion with careful attention to application of consistent standards across each area item being graded.

Table 3. Strength of evidence grades and definitions

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding judgment.

Applicability

We assessed applicability of the results gathered from the literature to the population of women with abnormal cyclic and irregular uterine bleeding according to EPC methods guidance.[48] Assessments of applicability were done to account for any factors limiting the ability to apply interventions to other populations or other settings, such as inadequate description of the intervention or failure to report followup data.

Using the patient, intervention, comparator, outcome, timing, and setting (PICOTS) framework, we identified factors that may limit the applicability of individual research studies. We summarized the applicability of the body of evidence and described key elements from the PICOTS framework that characterize the applicability of a body of studies.

Peer Review and Public Commentary

Experts in reproductive endocrinology and primary care treatment of women were invited to provide external peer review. The draft report was posted for 4 weeks to elicit public comment. We addressed all reviewer comments by revising the text as appropriate. Responses to peer and public review comments will be listed in the disposition of comments report. This report will be available on the AHRQ Web site 3 months after the posting of this final CER.

Results

Introduction

This chapter presents the results of the systematic review of the literature on primary care management of abnormal uterine bleeding (AUB). We present findings for Key Question 1 (KQ1) beginning with an overview of the content of the literature as a whole, followed by results and detailed analysis organized first by studies addressing irregular uterine bleeding (KQ1A) and then by studies addressing abnormal cyclic uterine bleeding (KQ1B). When there are distinct populations in which the interventions have been studied such as enrollment based on differing criteria, we discuss related data together. Within KQs we present summary information in the order: devices, medications, lifestyle and behavioral interventions, and complementary and alternative medicine. Within a category such as medication, we organize the results from greater number of studies to fewer, and presented the results of placebo controlled trials before direct comparisons. These analyses are followed by review of the studies and supplemental information addressing KQ2, which pertains to harms associated with the interventions identified for KQ1.

Studies also are described in summary tables, generally organized to present particular common outcomes, like change in volume of bleeding, in a single summary in the relevant section of text. Details on quality assessment and individual components of the quality scoring for individual studies can be found in Appendix I. Information about the overall strength of evidence supporting the effectiveness of specific interventions (or lack of utility) is summarized by related outcomes in the Discussion.

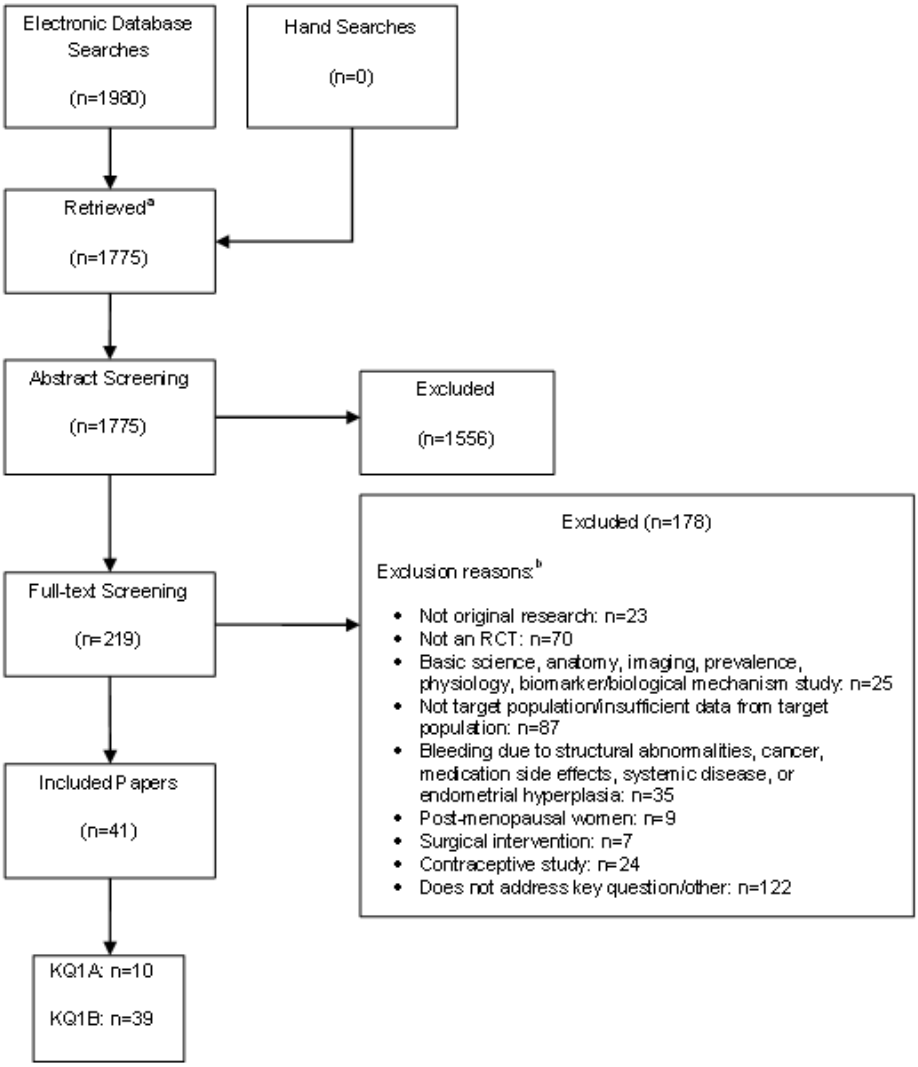
Results of Literature Searches

Searches identified 1,775 titles and abstracts for screening for KQ1. From this broad screening, we reviewed the publication abstracts and identified 219 publications as potentially eligible for inclusion. Following a review of the full text, we identified 39 studies described in 41 publications that met the predetermined criteria for inclusion. Publications from 10 studies addressed KQ1A. Thirty-one publications from 29 studies addressed KQ1B. Overall 6 of these studies were rated as good quality, 10 as fair, and 23 as poor with regard to risk of bias in the findings. Details of the scoring of individual publications are included in Appendix I.

We conducted a separate search and screening process for KQ2. We identified 2,730 titles and abstracts for screening. Of these, 788 references were promoted for full-text review. Using predefined criteria, we found 25 publications that were eligible for inclusion. We received 4 of 17 requested industry packets and obtained package inserts for each KQ1 included drug intervention. See Figures 2 (KQ1) and 3 (KQ2) for a diagram of literature search and screening.

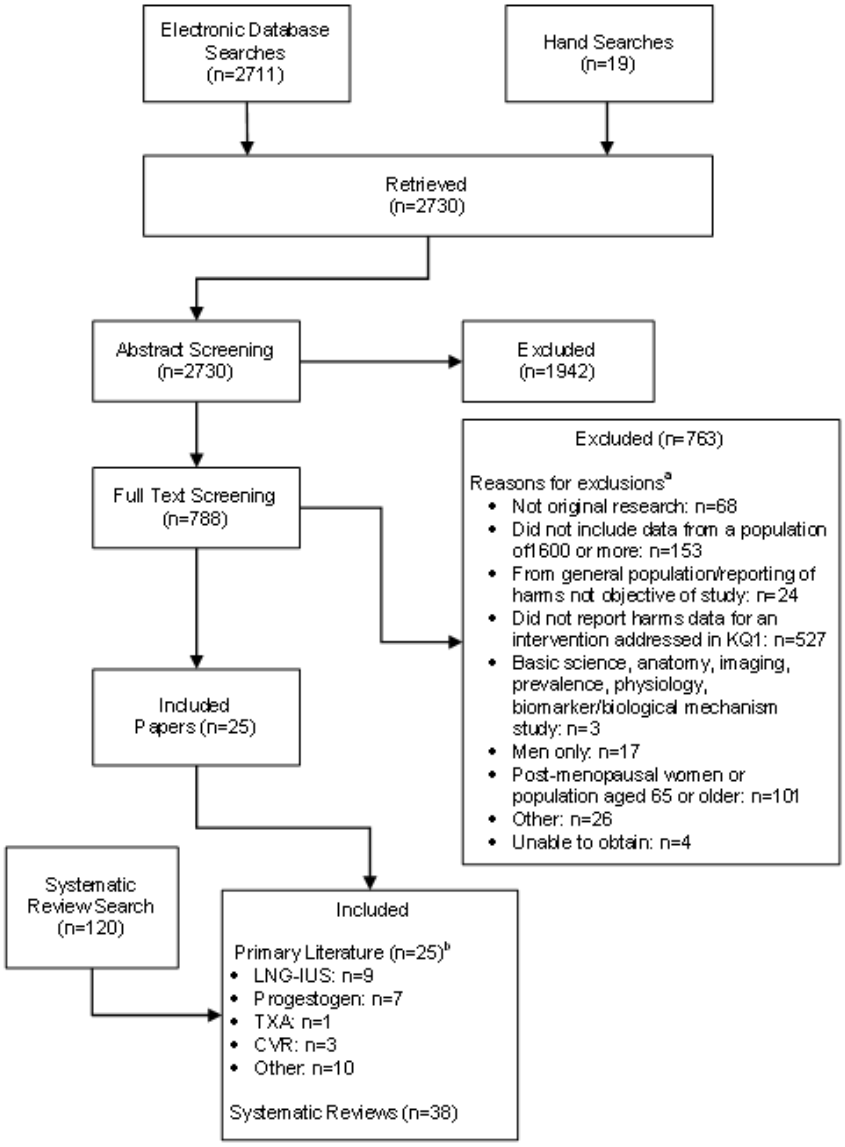
The complete list of excluded papers and exclusion reasons is provided in Appendix K for KQ1 and in Appendix L for KQ2.

Figure 2. Flow diagram of literature search and screening (KQ1)



KQ = Key Question; RCT = randomized controlled trial
[a]After duplicates removed.
[b]Total does not equal number excluded as publications could be excluded for multiple reasons.

Figure 3. Flow diagram of literature search and screening (KQ2)



KQ1 = Key Question 1; LNG-IUS = levonorgestrel-releasing intrauterine system; TXA = tranexamic acid; CVR = contraceptive vaginal ring

[a]Total does not equal number excluded as publications could be excluded for multiple reasons.

[b]Numbers do not tally as papers could include data on harms for more than one intervention.

Description of Included Studies

Included studies evaluated 12 different interventions including: levonorgestrel-releasing intrauterine system (LNG-IUS), nonsteroidal anti-inflammatory drugs (NSAIDs), combined oral contraceptives (COCs), tranexamic acid (TXA), contraceptive vaginal ring, metformin, exenatide, progestogens, cabergoline, lifestyle/behavioral changes, acupuncture, and decision aids using at least one comparator or placebo arm. Table 4 includes a complete list of the medications from the included studies. Twenty-one studies were head-to-head comparisons and 14 of the included studies established intervention efficacy by comparison to placebo. Four studies compared the intervention to usual or existing care. The majority of studies (29 studies reported in 31 publications) included in this review recruited women with complaints of abnormal cyclic uterine bleeding (KQ1B). Ten of the included studies targeted women with irregular uterine bleeding (KQ1A). Fourteen studies (36 percent) included some measure of patient reported outcome. Sixteen studies (41 percent) included some measure of symptom resolution or normalization.

The duration of the studies included in this review was generally short. Studies addressing KQ1A had a duration of 6 months or less with most (7/10) lasting 3 to 4 months. For KQ1B, study duration ranged from 2 cycles to 2 years. The majority of the studies (22/29) evaluating an intervention for abnormal cyclic bleeding lasted 6 months or less. Two studies that compared the effectiveness of LNG-IUS with COC lasted for 1 year. Of the two studies on the use of decision aids, one included a 1-year followup and the other included a 2-year followup.

We did not identify publications that explicitly focused on reducing heavy menstrual blood loss (MBL) in the context of irregular menses, especially menses with extended intervals between episodes of bleeding. The publications included for KQ1A are focused exclusively on irregular bleeding patterns, most often oligomenorrhea (fewer cycles than normal across months). Studies that met the criteria for inclusion for KQ1A evaluated progestogens (1 study),[49] COCs (1 study),[50] metformin (4 studies),[51-53,54] exenatide (1 study),[53] cabergoline (1 study),[55] diet (1 study),[56] and exercise (1 study),[57] and acupuncture (2 studies).[57,58] These total to more than 10 since several were direct comparisons. Two studies were good quality,[50,55] 2 were fair quality,[51,58] and 6 were poor quality.[49,52-54,56,57]

For KQ1B, most of the included studies evaluated LNG-IUS (7 studies),[59-65] NSAIDs (13 studies)[63,66-77] or TXA (7 studies).[66,71,77-81] We identified 5 studies[59,61,68,82,83] that evaluated the use of COCs for the management of AUB and 1 study of the contraceptive vaginal ring.[84] We found 3 studies[85-87] that evaluated decision aids for the management of AUB. Included studies evaluated the effect of these interventions on MBL, quality of life, menstrual cycle patterns, and other clinical and functional outcomes. Among the most common outcome metrics was change in MBL expressed as a percent. This was typically reported as a comparison of post-treatment blood loss to baseline. The alkaline hematin method and the pictorial blood loss assessment chart score were used to measure MBL. The alkaline hematin method, the current gold standard for estimating MBL, requires women to collect their used feminine hygiene products; consequently, it is rarely used outside of a research setting.[88,89] The pictorial blood loss assessment chart score is a practical, semi quantitative method of estimating MBL, in which women indicate the type of product used and the degree of saturation using a chart for guiding classification.[90-92]

For KQ2, we identified 23 publications reporting on harms of the included interventions. We also reviewed and summarized harms reported in the randomized controlled trials (RCTs) from KQ1 and from the package inserts for all products and prescription interventions included in KQ1.

Table 4. Medications from studies included in the CER

Medication	Brand Name
Levonorgestrel-releasing intrauterine system	Mirena®
Contraceptive vaginal ring	NuvaRing®
Antifibrinolytic Agents	
Tranexamic acid, oral	Lysteda®
Combined Oral Contraceptives, Oral	
Estradiol valerate and dienogest, oral	Natazia®
Ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg), oral	Nordette®, Altavera®, Levora®, Marlissa®, Portia® 28
Ethinyl estradiol (0.20 mg) and norethindrone acetate (1.0 mg), oral	Loestrin® 21 1/20, Junel® 1/20, Microgestin® 1/20, Minestrin® 1/20
Norgestimate ethinyl estradiol (triphasic), oral	Ortho Tri-Cyclen®, Tri-Sprintec®, Tri-Previfem®, MonoNessa®, Ortho Tri-Cyclen® Lo, Ortho-Cyclen®, Sprintec®, TriNessa®
Progestogens	
Dydrogesterone, oral	Gynorest® International brand names: Dabroston, Dufaston, Duphaston®, Terolut
Medroxyprogesterone acetate, injectable suspension	Depo-Provera® CI, Depo-subQ Provera 104
Medroxyprogesterone acetate, oral	Provera®
Norethisterone/norethindrone, oral	Aygestin®
Progesterone, vaginal gel	Crinone®
Nonsteroidal Anti-Inflammatory Drugs	
Flurbiprofen, oral	Ansaid®
Meclofenamate	Meclomen®
Mefenamic acid, oral	Ponstel®
Naproxen sodium, oral	Naprosyn®, Anaprox® DS, Anaprox®, Naprosyn® Suspension, EC-Naprosyn®, Various OTC brands
Other	
Cabergoline, oral	Dostinex®
Exenatide, injection	Byetta®
Ethamsylate, etamsylate	International brand names: Altodor, Dicinone, Dicynene, Dicynone, Eselin®, Ethamsyl, Hemo 141, Hemoced, Impedil
Metformin hydrochloride, oral	Glucophage®, Glucophage XR®, Fortamet®, Glumetza®

KQ1A. Management of Irregular Uterine Bleeding

Description of Included Studies

As noted in the description of the overall literature yield for this review, we did not identify publications that explicitly focused on mitigating the heaviness of irregular uterine bleeding. Symptoms like gushing or soaking type bleeding commonly occur in the context of irregular menses, especially menses with extended intervals between episodes of bleeding. The publications available to be included for this KQ focused on improving the regularity of bleeding and enrolled participants with bleeding categorized by the research teams as "dysfunctional uterine bleeding" or irregular bleeding with oligomenorrhea (i.e., fewer cycles than normal).

Studies were included whether or not participants reported menorrhagia (heavy bleeding) as long as the authors reported on the use of the intervention to improve cycle regularity. We did

not review the literature on infertility or subfertility resulting from absent or infrequent ovulation, even when it included cycle regularity data. Interventions for fertility treatment in this group, like clomiphene, are distinct from those for symptom management used in primary care settings. Likewise research populations of infertile women likely lack comparability to the broader population of women whose primary complaint is irregular cycles and may include women with subfertility who are seeking treatment for problem bleeding.

Overall 10 studies addressed restoring menstrual regularity in those with irregular uterine bleeding. Three were conducted in the United States,[50,53,56] two in Italy,[52,55] two in Turkey,[49,54] and one each in China,[58] Sweden,[57] and the United Kingdom.[51] The studies ranged in size from 23 to 201 participants and examined the efficacy of metformin (4 studies),[51-54] acupuncture (2 studies),[57,58] diet and exercise (1 study),[56] cabergoline (1 study),[55] progestogen (1 study),[49] and triphasic birth control pills (1 study).[50] Two studies were classified as good quality,[50,55] two as fair quality,[51,58] and six as poor quality[49,52-54,56,57] with respect to risk of bias in the assessment of effectiveness of the intervention of improving cycle regularity. Details of quality scoring for individual publications are included in Appendix I.

Overall these 10 studies, that included women with irregular uterine bleeding, offer incomplete evidence that medications, possibly diet and exercise, and potentially acupuncture may offer some benefit for establishing more predictable menstrual bleeding patterns. They provide no direct evidence about the ability to reduce the heaviness of bleeding or the symptoms and bother associated with intermittent heavy bleeding because quantity of bleeding and patient-reported outcomes other than timing of bleeding were not among the outcomes for these trials.

Key Points

- Metformin improves regularity of menstrual bleeding in women with polycystic ovarian syndrome (PCOS) when evaluated over months. When combined with exenatide, a newer injectable drug typically used for type 2 diabetes, the effect is greater than either metformin or exenatide alone over 6 months of followup in a single study of 60 women.
- In a very preliminary investigation of cabergoline, a drug typically used for elevated prolactin, three of eight women with PCOS and normal prolactin levels resumed regular cycles while none did in the six-person placebo group.
- Both oral dydrogesterone and vaginal micronized progesterone gel administered on a cyclic schedule had comparable influence on normalizing timing of menses.
- Triphasic norgestimate-ethinyl estradiol birth control pills provided excellent or good control of bleeding abnormalities in 68 percent of those taking active pills compared with 26 percent of those receiving placebo.
- In adolescents both a low-fat, calorie-restricted diet or a carbohydrate-restricted diet along with 30 minutes of anaerobic exercise 3 days a week resulted in more regular menses if the individual lost weight.
- Acupuncture improved cycle regularity in two trials, one in which both acupuncture and exercise (30 minutes 3 days each week) resulted in improvements by 32 weeks compared with placebo. In this study acupuncture provided more rapid relief by 16 weeks than exercise. Another poorly-described study found more individuals “cured” using needle placement specific for mind tranquilizing and menstruation promotion compared with those for delayed menses.
- In summary a number of available interventions appropriate for use in primary care settings have preliminary evidence of effectiveness for increasing the regularity of

menses. Only metformin consistently demonstrated benefit across studies and each of these studies enrolled women with oligomenorrhea and PCOS.
- Overall, literature is absent to inform choice of any of these modalities over another.

Detailed Synthesis

Medical Therapies

Seven studies, two conducted in the United States, two in Italy, two in Turkey, and one in the United Kingdom examined medical therapies to improve menstrual interval.[49-55] Five included women who met detailed criteria for PCOS[51-55] and two included women classified as having dysfunctional uterine bleeding by clinical criteria that are not tightly operationalized but include extended intervals between cycles.[49,50] We first present the findings for the RCTs that enrolled women with irregular uterine bleeding and then the data from PCOS trials.

Medical Therapies for Irregular Uterine Bleeding

Two studies, one comparing a triphasic oral contraceptive with placebo and one comparing vaginal micronized progesterone (8% gel) with oral dydrogesterone, evaluated medical therapy in women with irregular uterine bleeding (Table 5).

Table 5. Primary outcomes of medical interventions for irregular uterine bleeding

Author, Year Country Quality	Comparison Groups (n)	Key Cycle Control Outcomes
Davis et al., 2000[50] United States Good	**G1:** Triphasic norgestimate-ethinyl estradiol oral contraceptive (101) **G2:** Placebo (100)	• Study population included women with oligomenorrhea, menorrhagia, menometrorrhagia, and polymenorrhea. • Investigators classified resolution of bleeding abnormalities from diaries as excellent or good in 41.2% and 26.8% of those receiving intervention and 10.5% and 15.8% of those on placebo (p<0.001). • Women's self-assessments were similar to the investigators' and indicated better outcomes in those receiving the oral contraceptive (p<0.001).
Karakus et al., 2009[49] Turkey Poor	**G1:** Vaginal micronized progesterone, 90 mg every other night for 10 days (34) **G2:** Oral dydrogesterone, 10 mg daily for 10 days (35)	• Both groups achieved comparable regularity of bleeding patterns in the 3 treated cycles observed: 92.6%, 88.9%, and 92.6% in the vaginal group, and 81.5%, 88.9%, and 85.2% in oral group (p>0.5). • Satisfaction with intervention was comparable between groups (p=0.5).

Triphasic Oral Contraceptives

Oral contraceptives over-ride the hypothalamic-pituitary-ovarian axis coordination of ovarian sex steroid production. By providing exogenous estrogen and progestogen, oral contraceptives are intended to regulate cycle control pharmacologically. A single RCT[50] evaluated a triphasic norgestimate-ethinyl estradiol preparation compared with placebo among women classified as having dysfunctional uterine bleeding. Triphasic oral contraceptives have three distinct levels of progestogen (norgestimate in this study) and estrogen (ethinyl estradiol) over the course of the 21 days of active pills in a typical 28 day oral contraceptive pill pack, compared with monophasic pills which have the same hormone level provided across all 21 days of active pills.

The researchers randomized 201 women at a 1:1 ratio to receive either the study drug or placebo for three 28-day cycles. Data from 192 patients were included in the outcome analyses.

The study enrolled participants with a variety of menstrual concerns including heavy periods, frequent periods, irregular and heavy periods, and rare episodes of bleeding. Investigators did not systematically evaluate for the presence of disorders of hemostasis. The data are provided in aggregate for all participants regardless of their bleeding pattern or primary symptom. The study drug regimen included 0.18 mg norgestimate and 0.035 mg ethinyl estradiol for days 1 to 7, 0.215 mg norgestimate and 0.035 mg ethinyl estradiol for days 8 to 14, 0.25 mg norgestimate and 0.035 mg ethinyl estradiol for days 15 to 21, and inactive tablets for days 22 to 28. The primary efficacy outcomes included the investigator and the subject's overall assessment of improvement in AUB symptoms.

Both the investigator assessments and subject assessments of symptom improvement indicated significant ($p<0.001$) improvement in cycle control in the study drug group compared with the placebo group. The investigator assessed some level of subject improvement (fair, good, or excellent) in 81.4 percent of triphasic norgestimate ethinyl estradiol-treated patients as compared with 35.8 percent of placebo-treated patients; the proportions of subject-rated improvement were similar to investigator ratings. Among several quality of life measures assessed, improvement over baseline was only observed in physical functioning in the triphasic norgestimate ethinyl estradiol-treated patients compared with their placebo-treated counterparts.

This good quality, multicenter, industry-sponsored trial was conducted in the United States and appears to have been conducted to expand the indication for a particular brand name to include cycle control for women with dysfunctional uterine bleeding. The trial was published in 2000 and was the only study identified that included women with problem bleeding from irregular and closely spaced or rare menses.

Progestogens

Prior to menses without ovulation the sequence of biologic events that includes a rise in progesterone and then a precipitous drop does not occur. This is because the literal site of ovulation, the corpus luteum, is responsible for production of progesterone. In the absence of conception, the corpus luteum involutes and ceases production. This rise and fall in progesterone has multiple biological effects on the endometrium which include "organization" that results in a coordinated withdrawal bleed, the menses, after progesterone levels fall. Administration of a progestogen is intended therapeutically to mimic natural production of progesterone and then withdrawal.

A single RCT sought to compare the efficacy of oral dydrogesterone, 10 mg twice daily for 10 days starting on cycle day 15, compared with vaginal micronized progesterone (8 percent gel) applied every other evening from cycle days 17 to 27. Both groups had improvements in cycle regularity compared with their baseline (p value not provided).[49] Regular bleeding patterns were observed in more than 89 percent of the three treated cycles in the vaginal administration group, and more than 82 percent of the oral group. Improvement in bleeding patterns was comparable for both groups ($p>0.5$). Satisfaction with the intervention was also comparable across groups.

Medical Therapies for PCOS

Three medical therapies (metformin, exenatide, and cabergoline) were evaluated in five trials that enrolled women with PCOS (Table 6). We present the findings from the study of cabergoline followed by findings from four studies that evaluated metformin or exenatide. In summary, each of the studies of medical therapies reported findings that favor the medical intervention for establishing more predictable cycles in women with PCOS. No medication was effective for all participants though several exceeded 80 percent of those on active therapy

achieving improvements in cycle regularity. The number and size of studies is small and overall the quality is fair to poor with one small pilot study of good quality design and implementation but limited by lack of statistical power.

Table 6. Primary outcomes of medical interventions for irregular uterine bleeding in women with PCOS

Author, Year Country Quality	Comparison Groups (n)	Key Cycle Control Outcomes
Paoletti et al., 1995[55] Italy Good	**G1:** Cabergoline, 0.5 mg each week (8) **G2:** Placebo (6)	3 of 8 women receiving cabergoline resumed regular cycles. 5 of 8 had onset of menses within 32 to 37 days of treatment initiation. Among women receiving placebo 3 had no menses and 3 had menstrual cycles that were widely separated in time. (No statistical comparisons are provided.)
Fleming et al., 2002[51] United Kingdom Fair	**G1:** Metformin, 850 mg twice a day (45) **G2:** Placebo (47)	Mean time to first ovulation was shorter with metformin (23.6 days) than placebo (41.8 days) (p=0.02). Total ovulation events where higher among women receiving metformin over 16 weeks (p=0.59). Pregnancy rate not different among those who desired to conceive (4 of 23 in G1 and 1 of 19 in G2).
Oner and Muderriss 2011[54] Turkey Poor	**G1:** Metformin, 500 mg 3 times a day (50) **G2:** N-acetyl-cysteine, 600 mg 3 times a day (50)	Menstrual regularity improved significantly (p≤0.05) from baseline in G1 (from 17% to 47%) and G2 (from 29% to 53%). There was no significant difference in improvement from baseline between G1 and G2.
Elkind-Hirsch et al., 2008[53] United States Poor	**G1:** Exenatide, 10 mcg twice a day (20) **G2:** Metformin, 500 mg twice a day (20) **G3:** Both (20)	The combination of exenatide and metformin was superior to either medication alone for improving menstrual frequency. Women taking both had 80% of menses predicted for a normal pattern, compared with 57% (G1) and 49% (G2).
Moghetti et al., 2000[52] Italy Poor	**G1:** Metformin, 500 mg twice a day (11)[a] **G2:** Placebo (12)[a]	Study enrolled women with fewer than 6 menses per year and followed for 26 weeks. "Menstrual frequency" improved with metformin compared with placebo (p=0.002).

[a]total n=23; exact group size not specified.

Cabergoline

Cabergoline is a dopamine agonist used in treatment of pituitary adenomas, which are benign hormone producing growths in the pituitary often producing elevated prolactin levels. Mechanism of effectiveness for restoring cycles in PCOS may include amplifying dopamine neurotransmitter actions in the central nervous system resulting in hypoprolactinemia and lower levels of hormone signals that increase androgen production by the ovary.[55]

One good quality RCT[55] conducted in Italy evaluated cabergoline for improving menstrual cyclicity. In this preliminary study of 14 women, authors compared time to onset of menses and regularity of cycle in women treated with cabergoline (0.5 mg per week) with women receiving placebo. No statistical comparisons are reported, only the summary that five of the eight women receiving cabergoline had menses with three of them resuming regular cycles over 4 months. All women taking placebo had either no cycles (n=3) or widely spaced cycles (n=3).

Metformin and Exenatide

Metformin, the most common choice for initial type 2 diabetes management, reduces liver glucose production and increases uptake and use of glucose in other tissues throughout the body. Because relative insulin resistance is one of the manifestations of PCOS, metformin is believed

to disrupt this part of the syndrome by improving insulin response. Exenatide, a newer agent for treatment of type 2 diabetes introduced in 2005, is administered by subcutaneous injection. This drug promotes increased insulin release in response to blood glucose and it dampens glucagon activity. Glucagon is the natural hormone which promotes glucose release from storage in the liver. It is often administered as a second agent to improve glycemic control in those with type 2 diabetes. As metformin, it may improve the relative insulin resistance seen in PCOS.

One British[51] and one Italian[52] RCT evaluated metformin compared with placebo for improving menstrual cycle regularity among women with PCOS defined by rare or absent menstrual cycles, and hyperandrogenic chronic anovulation. The larger trial in the United Kingdom enrolled 82 women and randomly assigned them to an 850 mg dose twice a day. As with typical administration the dose was initiated at a lower level and increased over a week to reduce risk of gastrointestinal distress. Over the course of 16 weeks those on metformin ovulated sooner, an average of 18.2 days earlier (p=0.02), than those receiving placebo. Those on metformin also had a higher total number of ovulatory events (p=0.059). The Italian study (n=23), used a metformin dose of 500 mg 3 times a day (also after a ramp up) and reported "menstrual frequency" improved (p=0.002), without additional definitions of the outcome.

A poor quality trial (n=100)[54] in Turkey compared metformin (500 mg 3 times a day) to N-acetyl-cysteine (600 mg 3 times a day) for improving menstrual regularity in women with PCOS. Menstrual regularity improved significantly ($p \leq 0.05$) from baseline in both groups with no significant difference in improvement between groups.

A third trial in the United States compared three arms with 20 participants in each: metformin (500 mg twice each day), exenatide (10 mcg twice a day), and both.[53] Participants were followed for 6 months. The primary outcome for this trial was the proportion of menses achieved over time compared with what would be a predicted normal pattern. For instance a woman predicted to have six menses over 6.5 months would have a menstrual index of 50 percent if she in fact had only three menses over that time. Women taking metformin had 57 percent of expected menstrual bleeds and those on placebo had 49 percent. Those taking both metformin and exenatide had 80 percent of the predicted normal number of menses which was a significant advantage in effectiveness.

Behavioral Interventions

A single, poor quality study in teens with PCOS in the United States (n=24), attempted to examine the influence of diet and exercise on restoration of normal menses (Table 7).[56]

Table 7. Primary outcomes of behavioral interventions for irregular uterine bleeding in women with PCOS

Author, Year Country Quality	Comparison Groups (n)	Key Cycle Control Outcomes
Ornstein et al., 2011[56] United States Poor	**G1:** Hypocaloric low-fat diet (12) **G2:** Carbohydrate restriction without caloric or fat targets (12)	Both groups were asked to complete 30 minutes of aerobic exercise 3 times per week. Both lost similar amounts of weight over 12 weeks. Menstrual patterns are not reported by group. Amount of weight loss correlated with menstrual regularity.

Diet and Exercise

The rationale for examining the effects of diet and exercise is based on similar effects to the diabetes medications studied. Exercise improves glucose utilization and insulin sensitivity.

Likewise diet, with even modest weight loss, can improve insulin response. The study advised girls in both intervention groups to spend 30 minutes in aerobic activity 3 times each week. One arm was instructed in how to keep a hypocaloric diet, consisting of less than 40 grams per day of fat. The other group was instructed in how to follow a low-carbohydrate (i.e., no more than 20 grams per day) diet without specific calorie targets or fat restriction. Among the 16 who completed the study, both groups lost comparable amounts of weight over 12 weeks, an average of 6.5 percent of bodyweight. The authors did not report menstrual patterns by diet treatment group; they report only that degree of weight loss correlated with menstrual regularity ($r= -0.2$, $p=0.001$).[56]

Complementary and Alternative Medicine

Two trials, one of fair quality[58] and another of poor quality,[57] report on use of acupuncture for menstrual regularity among women with oligomenorrhea from PCOS and dysfunctional uterine bleeding, respectively (Table 8).

Table 8. Primary outcomes of acupuncture for irregular uterine bleeding

Author, Year Country Population Quality	Comparison Groups (n)	Key Cycle Control Outcomes
Cai and Wu, 2009[58] China Dysfunctional uterine bleeding Fair	**G1:** Acupuncture at points for mind tranquilizing and menstruation promotion (23) **G2:** Routine acupuncture points for delayed menses (17)	Based on self-reported scores, 67% of G1 were classified as cured compared with 19% of G2 over 3 cycles. 25% of G1 classified as markedly relieved compared with 19% of G2. There were no failures in G1 and 19% in G2 ($p<0.05$).
Jedel et al., 2011[57] Sweden PCOS Poor	**G1:** Low-frequency electroacupuncture (33) **G2:** Brisk exercise at least 30 minutes 3 days per week (34) **G3:** No active intervention (17)	Electroacupuncture achieved greater improvement in regularity (+146% from baseline) compared with G2 (58% improvement) and G3 (17% worsening). All comparisons $p<0.05$ at 16 weeks. By 32 weeks, electroacupuncture (+121% increase in cycle regularity) and exercise (+42%) were comparable and both superior to no intervention (−17%).

PCOS = polycystic ovarian syndrome

Acupuncture

The smaller study (n=40)[58] inadequately describes inclusion criteria specifying only that women were clinically diagnosed with dysfunctional uterine bleeding, and likewise operationalizes outcomes loosely by classifying participants as "cured" or not without providing a definition of what characteristics of the menstrual pattern or bleeding constituted a cure. The intervention of interest to the investigators was acupuncture for mind tranquilizing and menstruation promotion compared with a more conventional selection of needle sites used for delayed menses. Over three cycles more women were classified as cured using the mind-tranquilizing and menstruation promoting method (67% vs.19%); more women classified symptoms as markedly relieved, and there were no failures in the intervention compared with the usual approach arm (19%,, $p<0.05$).

The larger, poor quality study done in Sweden (n=84)[57] randomized participants to low-frequency electroacupuncture for a total of 14 treatments, brisk exercise 30 minutes 3 times each week, or no active intervention. At 16 weeks electroacupuncture achieved greater improvement in menstrual regularity, defined as a ratio of the number of observed versus expected cycles.

Women began the study with a ratio of 0.28 menses per expected cycle and improved in the electroacupuncture group to 0.69 menses per expected cycle a 146-percent increase in cycle regularity when compared with either exercise (58% improvement) or no active intervention (17% worsening) at 16 weeks. By 32 weeks, electroacupuncture (121% increase in cycle regularity) and exercise (42% increase in cycle regularity) were comparable and both superior to no intervention (17% decrease in cycle regularity).

KQ1B. Management of Abnormal Cyclic Bleeding

Description of Included Studies

We identified 31 publications representing 29 studies addressing primary care interventions for the management of abnormal cyclic uterine bleeding. Most of the studies that qualified for inclusion evaluated the LNG-IUS (7 studies),[59-65] NSAIDs (13 studies),[63,66-77] or TXA (7 studies).[66,71,77-81] We identified five studies[59,61,68,82,83] that evaluated use of COCs for the management of AUB and one study of the contraceptive vaginal ring.[84] We found three studies[85-87] that evaluated decision aids for the management of AUB. The total number of interventions addressed is greater than the number of studies because of direct comparisons between one or more interventions within single studies. Included studies described interventions appropriate for primary care and compared these interventions to another intervention (16 studies), placebo (9 studies), or usual care (4 studies). The results are summarized below and details for each study are presented in the Evidence Table (Appendix J).

Levonorgestrel-Releasing Intrauterine System (Mirena®)

Key Points

- LNG-IUS is associated with a clinically significant reduction in MBL ranging from 70 to 87 percent in studies lasting up to 1 year. However, there are no controlled longer-term followup studies.
- In comparison to progestogens, combined hormonal pills, and NSAIDs, LNG-IUS provided greater reduction in MBL.
- No head-to-head comparisons of LNG-IUS versus TXA were assessed. An indirect comparison of the percentage reduction and volume reduction in MBL suggests that LNG-IUS has a greater effect than TXA.

Detailed Synthesis

The LNG-IUS is an intrauterine, long-term, progestogen-only method of contraception licensed for 5 years of use. The system must be inserted and removed by a qualified practitioner, including primary care providers. The LNG-IUS has a T-shaped plastic frame with a rate-limiting membrane on the vertical stem that releases a daily dose of 20 micrograms of levonorgestrel into the endometrial space. The effects of the LNG-IUS are local and hormonal, including prevention of endometrial proliferation. The LNG-IUS is also licensed for the management of idiopathic menorrhagia or heavy menstrual bleeding.

Seven RCTs of LNG-IUS were included (Table 9).[59-65] The number of study participants ranged from 39 to 165. The total number of women assigned to LNG-IUS was 275; study endpoint outcome measures were reported for 255.

Criteria for participation varied among the studies. Three trials assessed MBL using the alkaline hematin method for study entry and required that women have a mean MBL of 80 ml or more for at least one[63,64] or two [60] cycles prior to randomization. One study required that study participants report a pictorial blood loss assessment chart score greater than 100 for two consecutive cycles. For one trial, the inclusion criterion was self-defined as “heavy menstrual bleeding", although mean MBL and pictorial blood loss assessment scores were reported at baseline.[59] For one trial the inclusion criterion was intention to undergo hysterectomy for AUB not due to a fibroid greater than 3 cm.[65] In one trial, the authors did not adequately describe the inclusion criteria, although organic causes were excluded.[62] Baseline median and mean MBL values differed among the studies.

The target intervention was the same for all seven trials: LNG-IUS (52 mg levonorgestrel, initial release rate 20 mcg per 24 hours). The comparator differed among the 7 trials. Two trials compared LNG-IUS to a COC, including continuous daily ethinyl estradiol (30 mcg)/levonorgestrel (150 mcg)[59] and cyclic monthly norethindrone acetate (1 mg)/ethinyl estradiol (20 mcg) for days 1 to 21.[61] Three trials compared LNG-IUS with a progestogen: single intramuscular injection of depot medroxyprogesterone acetate (DMPA) on the first day of the cycle,[62] oral tablet of medroxyprogesterone acetate (MPA; 5 mg) daily starting on the first day of the cycle,[62] oral MPA (10 mg) daily for 10 days each cycle starting on cycle day 16,[60] and norethisterone (5 mg) 3 times daily from cycle day 5 to 26 for three cycles.[64] One trial compared LNG-IUS with oral mefenamic acid (500 mg) 3 times daily for first 4 days of each cycle.[63] One trial assigned the patients in the control group to continue their preexisting medical treatment for excessive uterine bleeding or symptoms of dysmenorrhea, or both.[65]

The primary outcome of six of the LNG-IUS studies was change in blood loss. The alkaline hematin method was used to measure MBL in four trials.[59,60,63,64] One of these four reported both mean and median MBL.[60] Two studies only reported median MBL[63,64] and one study only reported mean MBL.[59] Two trials used the pictorial blood loss assessment score for the primary outcome measure.[61,62] Two trials used the pictorial blood loss assessment chart as a secondary outcome measure.[59,63] One study reported the proportion of women who cancelled their prior decision to undergo hysterectomy as the primary outcome measure.[65]

The timing of the summative outcome measure reporting varied among the trials. One trial reported after one menstrual cycle.[64] Three trials reported after three menstrual cycles.[60,63,64] Four trials reported after six menstrual cycles.[60,62,63,65] Two trials reported after 12 months.[59,61]

The setting varied: one trial was conducted in three countries (Brazil, Canada, and the United States);[60] two trials were conducted in the United Kingdom;[63,64] the remainder of studies were conducted in Egypt,[59] Canada,[61] Turkey,[62] and Finland.[65] Two studies were assessed as fair quality,[60,64] and five were of poor quality related to inadequate allocation concealment, lack of blinding of participants and assessors, and selective outcome reporting.[59,61-63,65] Details of quality scoring for individual publications are included in Appendix I.

Table 9. Primary outcomes of LNG-IUS for abnormal cyclic uterine bleeding

Author, Year Country Quality	Comparison Groups (n)	Key Outcomes
Kaunitz et al., 2010[60] United States, Canada, Brazil Fair	**G1:** LNG-IUS (82) **G2:** MPA,10 mg daily for 10 days of each cycle (83)	• Median reduction in MBL (alkaline hematin) was −128.7 ml in G1 compared with −17.8 ml in G2 after 6 cycles (p<0.001). • Higher proportion of women with successful treatment (defined as MBL<80 ml and 50% or greater reduction in MBL from baseline) in G1 (84.8%) compared with G2 (22.2%) (p<0.001).
Irvine et al., 1998[64] United Kingdom Fair	**G1:** LNG-IUS (22) **G2:** Norethisterone, 5 mg 3 times daily on cycle day 5 to 26 (22)	• MBL decreased significantly in both groups after 3 cycles (94% reduction for G1 and 87% reduction for G2). • More women in G1 (76%) wished to continue treatment after 3 months as compared with G2 (22%).
Shaaban et al., 2011[59] Egypt Poor	**G1:** LNG-IUS (56) **G2:** Low-dose COC, 30 mcg ethinyl estradiol and 150 mcg levonorgestrel (56)	• MBL assessed by alkaline hematin method significantly (p<0.001) decreased in both groups from baseline. • Greater reduction in MBL measured by alkaline hematin method at 12 months in G1 (87.4 ± 11.3%) compared with G2 (34.9 ± 76.9%) (p=0.01). • PBLAC scores decreased more in G1 (86.6 ± 17.0%) compared with G2 (2.5 ± 93.2%) at 12 months (p<0.001). • Women in G1 had significant improvements in ferritin and hemoglobin at 12 months. • Fewer bleeding days per year in G1 (34.5 ± 12.0) compared with G2 (65.1 ± 15.3) (p<0.001).
Endrikat et al., 2009[61] Canada Poor	**G1:** LNG-IUS (20) **G2:** COC, 1 mg norethindrone acetate and 20 mcg ethinyl estradiol (19)	• PBLAC score decreased significantly (p<0.001) in both groups at 12 months. • The MBL median score decreased more in G1 (from 228 to 13, −83% mean change) compared with G2 (from 290 to 72, mean change −68%) (p=0.002). • Proportion of women with successful treatment (defined as MBL score<100 at 12 months) higher in G1 (80%) compared with G2 (37%) (p<0.009). • Mean hemoglobin levels increased in both groups from baseline (p<0.001).
Kucuk and Ertan, 2008[62] Turkey Poor	**G1:** LNG-IUS (44) **G2:** DMPA, single shot (44) **G3:** MPA, 5 mg daily (44)	• More women in G1 (86%) with successful treatment compared with G2 (75%) or G3 (68%). • PBLAC scores, days of menstrual bleeding, and hemoglobin improved in all 3 groups from baseline. • Mean MBL scores at 6 months were lower in G1 (77) compared with G2 (146) and G3 (154) (p<0.01).

Table 9. Primary outcomes of LNG-IUS for abnormal cyclic uterine bleeding (continued)

Author, Year Country Quality	Comparison Groups (n)	Key Outcomes
Reid and Virtanen-Kari, 2005[63] United Kingdom Poor	**G1:** LNG-IUS (25) **G2:** Mefenamic acid, 500 mg 3 times per day for first 4 days of cycle (26)	• MBL significantly reduced in both groups from baseline. • After 6 months median MBL was 5 ml in G1 compared with 100 ml in G2 (p<0.001).
Lahteenmaki et al., 1998[65] Finland Poor	**G1:** LNG-IUS (28) **G2:** Usual care (28)	• Proportion of women cancelling hysterectomy was 64% in G1 vs. 14.3% in G2 (p<0.001).

COC = combined oral contraceptive; DMPA = depot medroxyprogesterone; LNG-IUS = levonorgestrel-releasing intrauterine system; MBL = menstrual blood loss; MPA = medroxyprogesterone; PBLAC = pictorial blood loss assessment chart

Description of Results

Outcome Measures

All but one of the LNG-IUS studies reported MBL using the alkaline hematin method or pictorial blood loss assessment score as the primary outcome. Four trials[59,60,63,64] used the alkaline hematin method to measure MBL and four trials used the pictorial blood loss assessment chart to estimate blood loss.[59,61-63] Two studies also reported treatment success as an outcome, defined as MBL less than 80 ml[60] or pictorial blood assessment score less than 100.[61] One trial reported the proportion of women who cancelled their prior decision to undergo hysterectomy as the primary outcome measure.[65] Other outcome measures reported in the studies of LNG-IUS included total bleeding and spotting days, hemoglobin, ferritin, treatment failure, and menorrhagia severity score.

Menstrual Blood Loss

Reduction Expressed as a Percent

Three studies reported the percent reduction in MBL from baseline (Table 10). A fair quality multicenter trial with 165 participants compared LNG-IUS with oral MPA administered during the luteal phase of the cycle and reported a mean reduction in MBL of 71 percent (SD ± 88%) in the LNG-IUS group compared with 22 percent (SD ± 36%) in the MPA group at the 6-month interval (p<0.001).[60] In a small fair quality RCT conducted in the United Kingdom,[64] the change in MBL was comparable between groups after 3 months of treatment with a 94-percent reduction in MBL for LNG-IUS users and an 87-percent reduction in MBL among women taking norethisterone.

A trial conducted in Egypt with 112 participants compared LNG-IUS with continuous combined ethinyl estradiol (30 mcg) and levonorgestrel (150 mcg; continuous COC) and reported an 87-percent (SD ± 12%) reduction in mean MBL in the LNG-IUS group compared with a 35-percent (SD ± 77%) reduction in the COC group at the 12-month interval (p=0.013).[59]

Table 10. Percent change in blood loss from baseline in studies of LNG-IUS

Author, Year	Comparator	LNG-IUS Group	Comparator Group	LNG-IUS vs. Comparator
Kaunitz et al., 2010[60]	MPA[a]	−70.8	−21.5	p<0.001
Irvine et al., 1998[64]	Norethisterone[b]	−94.0	−87.0	p=NS
Shaaban et al., 2011[59]	COC, continuous[c]	−87.4	−34.9	p=0.013

COC = combined oral contraceptive; MPA = medroxyprogesterone
[a]Oral medroxyprogesterone acetate (10 mg) once daily for 10 consecutive days starting on day 16 in each cycle.
[b]5 mg 3 times daily from day 5 to 26 of the cycle over three cycles.
[c]Ethinyl estradiol (30 mcg) and levonorgestrel (150 mcg).

Reduction Expressed as a Volume

Four studies reported the absolute reduction in MBL from baseline (Table 11). The multicenter trial with 165 participants reported a statistically significant (p<0.001) reduction in median MBL after six menstrual cycles with LNG-IUS (128.8 ml) compared with those receiving MPA (17.8 ml).[60]

The United Kingdom trial with 44 participants and 3 months duration reported similar reductions (p=NS) in median MBL for the LNG-IUS group (104 ml) and the norethisterone group (94 ml).[64]

The trial conducted in Egypt with 112 participants that compared LNG-IUS with continuous COC reported a statistically significant (p<0.001) reduction in mean MBL after 12 menstrual cycles with LNG-IUS (255.6 ml) compared with those receiving COC (156.1 ml).[59] A trial conducted in the United Kingdom with 51 participants that compared continuous LNG-IUS with mefenamic acid for the first 4 days of each cycle reported a statistically significant (p<0.001) difference in reduction in median MBL after six menstrual cycles with LNG-IUS (117 ml) compared with those receiving mefenamic acid (21 ml).[63] The same study reported a statistically significant reduction in median pictorial blood loss assessment chart score: a 215 point reduction after six cycles with LNG-IUS compared with a 74-point reduction with mefenamic acid (p<0.001).[63]

Table 11. Change in blood loss volume from baseline in studies of LNG-IUS

Author, Year	Comparator	LNG-IUS Group	Comparator Group	LNG-IUS vs. Comparator
Kaunitz et al., 2010[60]	MPA	−128.8 ml	−17.8 ml	p<0.001
Irvine et al., 1998[64]	Norethisterone	−104.0 ml	−94.0 ml	p=NS
Shaaban et al., 2011[59]	COC, continuous	−255.6 ml	−156.1 ml	p<0.001
Reid and Virtanen−Kari, 2005[63]	Mefenamic acid	−117.0 ml	−21.0 ml	p<0.001

COC = combined oral contraceptive; MPA = medroxyprogesterone
[a]Oral medroxyprogesterone acetate (10 mg) once daily for 10 consecutive days starting on day 16 in each cycle.
[b]5 mg 3 times daily from day 5 to 26 of the cycle over three cycles.
[c]Ethinyl estradiol (30 mcg) and levonorgestrel (150 mcg).

Pictorial Blood Loss Assessment Chart Score

Four studies reported change in pictorial blood loss assessment chart score from baseline. A poor quality Canadian trial with 39 participants compared LNG-IUS with 20 mcg ethinyl estradiol and 1 mg norethindrone acetate (cyclic COC) and reported an 83-percent reduction in the mean pictorial blood loss assessment chart score in the LNG-IUS group (median scores

declined from 228 to 12) compared with a 68-percent reduction in the cyclic COC group (median scores declined from 290 to 72) at 12 months.[61]

Another poor quality Turkish study of 132 women compared LNG-IUS use with either a single intramuscular injection of DMPA or with daily oral MPA. After 6 menstrual cycles, the LNG-IUS users had a mean score reduction of 210 compared with a reduction of 138 in the DMPA group ($p<0.01$), and a 76-point reduction in the MPA group ($p<0.01$). No significant difference was reported in the reductions in the pictorial blood loss assessment chart score between DMPA and MPA.[62]

The pictorial blood loss assessment was used in two trials that also measured MBL using the alkaline hematin method. One study reported a reduction in the mean pictorial blood loss assessment chart score of 90 percent (SD ± 12%) in the LNG-IUS group at the 6-month interval compared with a reduction of 42 percent (SD ± 54%) in the COC group.[59] At 12 months, the mean scores declined by 275 (87%) for LNG-IUS users compared with only 51 (3%) for the women taking COCs.[59] In another study, the change in median pictorial blood assessment scores from baseline was significantly greater ($p<0.001$) in the LNG-IUS group from 240 (range, 91 to 545) to 25 (range, 0 to 401) compared with the mefenamic acid group from 233 (range, 77 to 469) to 159 (range, 50 to 307) after six cycles of treatment. [63]

Treatment Success

Three studies reported the percent of women with successful treatment; however the definition of success differed among the trials. The fair quality multicenter trial with 165 participants that compared LNG-IUS with oral MPA reported a 85 percent (67/79) success rate in the LNG-IUS group at the 6-month interval, compared with a 22 percent (18/81) success rate in the MPA group ($p<0.001$).[60] Treatment success was defined as MBL less than 80 ml at the end of study and 50 percent or greater reduction in MBL from baseline.[60]

The poor quality Canadian trial with 39 participants that compared LNG-IUS with cyclic COC reported a treatment success of 80 percent (16/20) in the LNG-IUS group at the 12-month interval compared with 37 percent (7/19) in the cyclic COC group ($p<0.009$).[61] Treatment success was defined as a pictorial blood loss assessment chart score less than 100 at 12 months.[61]

The poor quality Turkish study that compared LNG-IUS with DMPA injection or oral MPA use reported treatment success rates of 86 percent, 75 percent, and 68 percent, respectively.[62] The criterion for determining treatment response was a pictorial assessment bleeding score less than 185 and stabilization or increase in hemoglobin levels.[62]

Total Bleeding Days and Total Spotting Days

The trial conducted in Egypt with 112 participants that compared LNG-IUS with continuous COC did not report baseline days of bleeding or spotting. The study did report that the endpoint number of bleeding days, adjusted for 1-year duration was 34.5 ± 12.0 for the LNG-IUS group and 65.1 ± 15.3 for the continuous COC group ($p<0.001$). The study also reported that the endpoint number of spotting days, adjusted for 1-year duration, was not different between the two groups.[59]

The trial conducted in Turkey with 132 participants that compared LNG-IUS with either a single intramuscular injection of DMPA or with daily oral MPA reported a statistically significant decrease in mean bleeding days after six menstrual cycles with all three interventions. No significant difference was reported in the decrease in bleeding days between LNG-IUS and DMPA and MPA.[62]

Hemoglobin

The trial conducted in Turkey with 132 participants that compared LNG-IUS with either a single intramuscular injection of DMPA or with daily oral MPA reported a statistically significant increase in hemoglobin after six menstrual cycles with all three interventions. The mean hemoglobin score was increased by 0.8 g/dl in the LNG-IUS group compared with 0.5 g/dl with DMPA ($p<0.05$) and compared with 0.6 g/dL with MPA ($p<0.05$). No significant difference was reported in the increase in hemoglobin between DMPA and MPA.[62]

The trial conducted in Egypt with 112 participants that compared LNG-IUS with continuous COC reported a statistically significant ($p<0.001$) increase in hemoglobin for the LNG-IUS group (1.2 g/dl) compared with the continuous COC group (−0.4 g/dl).[59] The United Kingdom trial with 44 participants reported no significant differences in hemoglobin changes over 3 months.[64] The Canadian trial with 39 participants that compared LNG-IUS with cyclic COC reported no significant differences in hemoglobin changes.[61]

Ferritin

The trial conducted in Egypt with 112 participants that compared LNG-IUS with continuous COC reported a statistically significant ($p<0.001$) increase in ferritin for the LNG-IUS group (56.7 mcg/dl) compared with the continuous COC group (−34.3 mcg/dl).[59] The United Kingdom trial with 44 participants and 3 months duration reported no significant differences in ferritin changes.[64]

Treatment Failure

The trial conducted in Egypt with 112 participants that compared LNG-IUS with continuous COC defined treatment failure as initiation of an alternative medical treatment or need for surgery or expulsion of the LNG-IUS. The trial reported a statistically significant ($p=0.007$) lower failure rate for the LNG-IUS group compared with the continuous COC group (hazard ratio= 0.30; 95% CI, 0.14 to 0.73).[59]

Proportion of Women Who Cancelled Hysterectomy

An open randomized multicenter study conducted in Finland with 56 women aged 33 to 49 scheduled to undergo hysterectomy for treatment of excessive uterine bleeding reported that 64 percent (95% CI, 44 to 81%) of women in the LNG-IUS group compared with 14 percent (95% CI, 4 to 33%) of women in the control group (continued current medical treatment) had cancelled their decision to undergo hysterectomy after 6 months ($p<0.001$).[65]

Head-to-Head Comparisons

LNG-IUS Versus COC

Both the trial that compared LNG-IUS to continuous COC (daily 30 mcg of ethinyl estradiol and 150 mcg levonorgestrel)[59] and the trial that compared LNG-IUS to cyclic COC (1 mg norethindrone acetate and 20 mcg ethinyl estradiol for days 1 to 21)[61] found that LNG-IUS was superior to COC for blood loss reduction expressed as a percent (83 to 90% reduction in mean pictorial blood loss assessment chart score for LNG-IUS compared with 42 to 68% for COC). One trial reported superiority of LNG-IUS for blood loss expressed as volume, total bleeding days, treatment failure, hemoglobin, and ferritin level.[59] One of the trials reported superiority of LNG-IUS for achieving blood loss below the definition of heavy menstrual bleeding.[61]

LNG-IUS Versus Progestogens

The only outcome measure used by all three trials that compared progestogens to LNG-IUS was MBL reduction by volume.[60,62,64] Two trials reported that LNG-IUS significantly reduced MBL compared with progestogens, including oral MPA (10 mg daily for 10 days starting on cycle day 16[60] or 5 mg daily starting on cycle day 1[62]) and DMPA (single injection of on cycle day 1).[62] A third trial reported no significant difference between LNG-IUS and norethisterone (5 mg 3 times daily from cycle day 5 to cycle day 26 for three cycles) for reducing MBL.[64] The trials used different progestogen formulations and different measures of blood loss.[60,62,64] One of the trials comparing LNG-IUS to oral MPA reported significantly greater treatment success, reduction in blood loss as a percentage, and women achieving blood loss less than the definition of heavy menstrual bleeding in the LNG-IUS group.[60]

LNG-IUS Versus Mefenamic Acid

A single trial reported significantly greater reduction in MBL for LNG-IUS (117 ml) compared with mefenamic acid (500 mg 3 times daily for first 4 days of cycle; 21 ml).[63]

Prevention of Hysterectomy

A single poor quality trial reported significantly more ($p<0.001$) women cancelled their decision to undergo hysterectomy in the LNG-IUS group (64%; 95% CI, 44 to 81%) compared with women who continued current medical treatment (14%; 95% CI, 4 to 33%).[65]

Contraceptive Vaginal Ring

Key Points

- A single RCT reported that the contraceptive vaginal ring was as effective as norethisterone for improving bleeding.
- More women who were randomized to the vaginal ring were satisfied with treatment compared with women randomized to norethisterone.
- More women in the vaginal ring group elected to continue treatment than in the oral medication group.

Detailed Synthesis

We identified a single RCT of fair quality that compared the efficacy of the contraceptive vaginal ring to norethisterone in 95 women with abnormal cyclic uterine bleeding (Table 12). The study was conducted in Egypt among women with a pictorial blood loss assessment chart score over 185. The primary outcome measure was MBL after three cycles of treatment assessed using the pictorial blood loss assessment chart score. Other outcome measures included duration of menses, hemoglobin, ferritin, and quality of life.

The treatments were equally effective, reducing the patient-reported bleeding score by 67 percent in the contraceptive vaginal ring group and by 70 percent in the norethisterone group.[84]

Table 12. Primary outcomes of contraceptive vaginal ring for abnormal cyclic uterine bleeding

Author, Year Country Quality	Comparison Groups (n)	Key Outcomes
Abu Hashim et al., 2012[84] Egypt Fair	**G1:** Contraceptive vaginal ring, 15 mcg of ethinyl estradiol and 120 mcg etonogestrel inserted between day 1 and 5 of cycle and used for 3 weeks/cycle (48) **G2:** Norethisterone acetate tablets,5 mg 3 times daily on days 5 to 26 (47)	• Mean PBLAC score declined significantly (p<0.001) from baseline after 3 cycles for G1 (from 288 to 90) and G2 (from 302 to 92). • Mean hemoglobin levels increased from baseline for both G1 (p=0.02) and G2 (p=0.03). • Duration of menses was significantly shorter (p<0.001) for both G1 and G2. • More women in G1 (71%) than in G2 (42.5%) were satisfied with treatment. • More women in G1 (77%) than in G2 (25.5%) elected to continue treatment.

PBLAC = pictorial blood loss assessment chart; MBL = menstrual blood loss

Nonsteroidal Anti-Inflammatory Drugs

Key Points

- The most commonly studied NSAID was mefenamic acid; other NSAIDs included naproxen, meclofenamate, and flurbiprofen.
- Overall, NSAIDs demonstrated significant reductions in MBL (20 to 49 percent) compared with baseline and were significantly more effective than placebo, but many women still have objective menorrhagia after treatment. Variability in treatment response with NSAIDs is considerable, including some individuals with increases in MBL with treatment.
- Comparing individual NSAIDs, there were no significant differences found in reductions of MBL between mefenamic acid and naproxen.
- In one RCT, LNG-IUS was significantly more effective at reducing MBL compared with mefenamic acid.
- In two trials, TXA had significantly greater reductions in MBL compared with either flurbiprofen or mefenamic acid.
- There were no significant differences between NSAIDs and either norethisterone, low-dose COC, ethamsylate, or an older progesterone-impregnated intrauterine coil in 5 trials.
- Studies were mostly of short duration with most lasting from 2 to 3 cycles.
- No studies examined quality of life, sexual function, fertility, or time to conception as an outcome. Quality of life needs further attention since most women will be offered treatment based on complaints/perception rather than objective measurement.
- NSAIDs are also effective against menstrual-related abdominal pain and cramping.

Detailed Synthesis

We identified 13 unique studies from 14 publications that examined the use of NSAIDs for abnormal cyclic uterine bleeding (Table 13). Seven were parallel group RCTs[63,66,67,69,70,74,77] and six were randomized, crossover trials.[68,71-73,75,76] Trials were conducted in seven different countries: Australia,[68,76] Canada,[73] India,[69,77] the Netherlands,[67] Sweden,[71] United Kingdom,[63,66,70,74,75] and the United States.[72] The number of participants in each trial ranged from 19 to 110 with crossover trials ranging from 14 to 69. One study was assessed as good quality,[72]

three were assessed as fair quality,[67,75,76] and nine were assessed as poor quality.[63,66,68-71,73,74,77] Details of quality scoring for individual publications are included in Appendix I.

Studies used different inclusion criteria for defining menorrhagia. Six trials used the objective alkaline hematin method with MBL more than 80 ml as criteria for inclusion.[63,66,67,70,71,75] Two trials used the alkaline hematin method with MBL more than 50 to 60 ml,[72,74] one study used a combination of subjective and objective assessments of MBL more than 80 ml,[73] and four trials used either subjective criteria or did not define heavy menstrual bleeding for inclusion into the trial.[68,69,76,77] Some studies required women to have regular cycles.[63,67,68,72,73,77] Most studies excluded populations who had underlying disease or intrauterine device (IUD) use. One study[76] included patients with IUD (n=6), fibroids (n=2), Von Willebrand disease (n=1) and reported changes in MBL separately for women with ovulatory menorrhagia from those with underlying disease. Another study also included patients with IUDs (n=7) in the eligible patient population.[72] Patients ranged in age from 14 to 51 years of age.

The target intervention differed among the 13 studies. For each NSAID, dose and duration did not vary greatly. The most commonly studied NSAID, mefenamic acid, was used in 11 trials.[63,66-70,73-77] The usual dose of mefenamic acid was 500 mg 3 times a day starting at the onset of menses for duration of 5 days or until cessation of menses. One study initiated mefenamic acid 5 days prior to onset of menses through cessation.[67] Another trial used a slightly different regimen with 500 mg at onset of menses followed by 250 mg every 6 hours for 3 to 5 days.[73] One study included mefenamic acid at 250 mg 3 times a day from onset menses for 5 days in conjunction with TXA 500 mg 3 times a day for the same 5-day period.[77] One trial studied meclofenamate at a dose of 100 mg 3 times a day from onset of menses for duration of 6 days or until cessation of menses.[72] Naproxen was studied in two trials with initial loading doses of 500 to 550 mg then 250 to 275 mg every 6 hours for 5 days or until 24 hours after cessation of heavy bleeding.[68,75] Flurbiprofen was studied in one trial at a dose of 100 mg twice a day from onset of menses for duration of 5 days.[71]

The comparator differed among the 13 studies. Mefenamic acid was compared with placebo in four studies, two RCTs[67,69] and two crossover trials.[73,76] One crossover trial compared meclofenamate to placebo.[72] Two crossover trials compared mefenamic acid to naproxen[68,75] for two cycles. One of these crossover trials also used low-dose COC with 30 mcg ethinyl estradiol and 150 mcg levonorgestrel given daily for 21 days for two cycles.[68] Two RCTs used norethisterone 5 mg twice daily from day 19 to 26 of the cycle[70] or days 15 to 25 of the cycle[74] for two cycles. Two RCTs used progesterone-releasing intrauterine systems, including the LNG-IUS that releases 20 mcg of levonorgestrel per day for six cycles[63] and an older progesterone-impregnated intrauterine coil that releases 65 mcg of progesterone daily for two cycles.[74] One RCT compared mefenamic acid (500 mg every 8 hours) with TXA (1 gram every 6 hours) and ethamsylate (500 mg every 6 hours) for the first 5 days of menses for three cycles.[66] One crossover trial compared flurbiprofen (100 mg twice a day for 5 days) with 1.5 grams of TXA (3 times a day for the first 3 days of menses and 1 gram on days 4 to 5) for two cycles.[71] One RCT compared a combination of mefenamic acid (250 mg per day) and TXA (500 mg 3 times a day) to TXA alone from day 1 to 5 of menses for three cycles.[77]

Duration of treatment ranged from one[67] to six[63] menstrual cycles, with the majority consisting of two[68,70-76] to three[66,69,77] cycles.

The primary outcome for most studies (11/13) was MBL measured with the alkaline hematin method.[63,66-68,70-76] Seven studies reported mean MBL[66-68,71-73,76] and four studies reported median MBL.[63,70,74,75] One small, placebo-controlled crossover trial[73] measured MBL but only

reported the proportion of women who experienced reductions in MBL during the treatment cycles. One trial used the pictorial blood loss assessment chart score[77] as the primary outcome measure for blood loss and a second trial of NSAIDS used the pictorial blood loss assessment chart as a secondary outcome measure.[63] One trial reported the percentage of patients relieved of menorrhagia,[69] however the method of measurement was not provided. Other outcomes studied included duration of bleeding,[66,69,70,72,75,76] number of pads/tampons used,[66,69,72,75] and total menstrual fluid loss.[63] One trial examined patient satisfaction.[66] No studies examined quality of life, sexual function, fertility, or time to conception as an outcome.

Table 13. Primary outcomes of NSAIDs for abnormal cyclic uterine bleeding

Author, Year Country Quality	Comparison Groups (n)	Key Outcomes
Vargyas et al., 1987[72] United States Good	**G1[a]:** Meclofenamate, 100 mg 3 times daily for 2 cycles followed by placebo for 2 cycles (15) **G2:** Placebo for 2 cycles, followed by meclofenamate for 2 cycles (17)	• Mean MBL during meclofenamate cycles (69.0 ± 6.3 ml) was significantly less than baseline (141.6 ± 15.9 ml) and during placebo cycles (135.6 ± 11.3 ml) (p<0.0001). • Mean number of bleeding days was shorter during meclofenamate cycles (4.8 ± 0.2) than during placebo cycles (5.4 ± 0.18) (p<0.0003). • Median hemoglobin, hematocrit, and serum ferritin levels did not change during the study.
Van Elijkeren et al., 1992[67] Netherlands Fair	**G1:** Mefenamic acid, 500 mg 3 times daily (6) **G2:** Placebo (5)	• Mean MBL decreased 40% in G1 from baseline mean 108 ml to 65 ml (p=0.01) compared with increase in G2 from 151 ml to 189 ml (p=0.46). • Patients were scheduled for hysterectomy.
Hall et al., 1987[75] United Kingdom Fair	**G1:** Mefenamic acid 500 mg every 8 hrs. in phase 1 and naproxen in phase 2 (19)[a] **G2:** Naproxen 550 mg loading dose followed by 275 mg every 6 hrs. in phase 1 followed by mefenamic acid in phase 2 (19)[a]	• Treatment with mefenamic acid and naproxen reduced bleeding by average of 47 and 46% respectively.
Fraser et al., 1981, 1984[76,93] Australia Fair	**G1:** Mefenamic acid, 500 mg 3 times daily for 2 cycles followed by placebo for 2 cycles (38)[a] **G2:** Placebo for 2 cycles followed by mefenamic acid (31)[a]	• Mefenamic acid significantly reduced mean MBL (28%) compared with placebo (p<0.001). • Reductions were greater (30%) among women with MBL >80 ml at baseline (p<0.001). • Only 30 out of 69 women had measured blood loss >80 ml during placebo cycles.
Najam et al., 2010[77] India Poor	**G1:** TXA, 500 mg and mefenamic acid, 250 mg 3 times daily (55) **G2:** TXA, 500 mg 3 times daily (55)	• The mean PBLAC score in G1 declined from 246 to 100 at 6 months (p<0.01) and in G2 from 250 to 125 (p=NS). • Hemoglobin levels significantly increased in both groups, from 8.6 to 12.3 in G1 (p=0.016) and from 9.5 to 12.0 in G2 (p=0.04).
Reid and Virtanen-Kari, 2005[63] United Kingdom Poor	**G1:** LNG-IUS (25) **G2:** Mefenamic acid 500 mg 3 times daily for first 4 days of cycle (26)	• MBL significantly reduced in both groups from baseline but after 6 months median MBL was 5 ml in G1 compared with 100 ml in G2 (p<0.001).

Table 13. Primary outcomes of NSAIDs for abnormal cyclic uterine bleeding (continued)

Author, Year Country Quality	Comparison Groups (n)	Key Outcomes
Bonnar and Sheppard, 1996[66] Ireland Poor	**G1:** Mefenamic acid, 500 mg (25) **G2:** TXA, 1 g (27) **G3:** Ethamsylate, 500 mg (29)	• TXA reduced MBL by 54% (mean decreased from 164 ml to 75 ml) and mefenamic acid reduced MBL by 20% (from 186 ml to 148 ml). Ethamsylate did not reduce MBL. • Mean MBL for women in G1 remained >80 ml after 3 treatment cycles (148 ml; range, 138 to 168 ml). • 77% in G2 and 74% in G1 wished to continue treatment. • Improvement in dysmenorrheal was reported by 19% in G1, 13% in G2 and 4% in G3.
Fraser and McCarron, 1991[68] Australia Poor	**G1:** Mefenamic acid, 500 mg every 6 to 8 hrs. for 2 cycles; naproxen, 500 mg at onset followed by 250 mg every 6 to 8 hrs. for 2 cycles (15)[a] **G2:** Mefenamic acid, 500 mg every 6 to 8 hrs. for 2 cycles; low-dose COC (ethinyl estradiol 30 mcg and levonorgestrel 150 mcg) for 2 cycles (15)[a]	• Mefenamic acid reduced MBL by 38% in G2 (p=0.002) and by 20% in G1 (p=0.198). • Women treated with low-dose COC had 43% reduction in MBL (p<0.001). • Naproxen resulted in a 12% reduction in MBL (p=0.079).
Grover et al., 1990[69] India Poor	**G1:** Mefenamic acid, 500 mg, every 8 hours (40)[a] **G2:** Placebo (40)[a]	• 86% of women in G1 reported relief of menorrhagia compared with 20% in G2 (p<0.001). • Mean bleeding days in G1 reduced from 9.7 ± 3.1 to 4.1 ± 0.6.
Cameron et al., 1990[70] Scotland Poor	**G1:** Mefenamic acid, 500 mg 3 times daily (17) **G2:** Norethisterone, 5 mg twice daily (15)	• Median blood loss was significantly reduced in both groups from 123 ml to 81 ml in G1 (p<0.001) and from 109 ml to 92 in G2 (p<0.002). • Median percentage reduction in blood loss was 24% for G1 and 20% for G2 (p>0.1). • 52% of women in G1 and 67% in G2 still had menorrhagia after 2 months of treatment.
Andersch et al., 1988[71] Sweden Poor	**G1:** Flurbiprofen, 100 mg twice daily for 2 cycles followed by TXA for 2 cycles (15)[a] **G2:** TXA, 1.5 g 3 times daily on days 1 to 3 and 1 g twice daily on days 4 to 5 for 2 cycles followed by flurbiprofen for 2 cycles (15)[a]	• Both treatments significantly reduced MBL (p<0.01). • Reduction in MBL was 53% with TXA compared with 24% for flurbiprofen (p<0.01). • Mean MBL reduced to 155 ± 33 ml with TXA and 223 ± 44 ml for flurbiprofen (baseline MBL was 295 ± 52 ml). • Hemoglobin did not change with either treatment.

Table 13. Primary outcomes of NSAIDs for abnormal cyclic uterine bleeding (continued)

Author, Year Country Quality	Comparison Groups (n)	Key Outcomes
Tsang et al., 1987[73] Canada Poor	**G1:** Mefenamic acid, 500 mg at onset followed by 250 mg every 6 hrs. for 3 to 5 days for 2 cycles followed by placebo (14)[a] **G2:** Placebo for 2 cycles followed by mefenamic acid for 2 cycles (14)[a]	• 8/10 women experienced reduction in MBL while taking mefenamic acid compared with placebo (p<0.05).
Cameron et al., 1987[74] United Kingdom Poor	**G1:** Mefenamic acid, 500 mg 3 times daily (8) **G2:** Norethisterone, 5 mg twice daily (8) **G3:** Progesterone-impregnated intrauterine coil releasing 65 mcg daily (8)	• Median MBL reduced in G1 from 68 to 47 ml (p=0.05) and in G3 from 71 to 45 ml (p<0.05). • Median MBL was unchanged in G2 (94 to 110 ml).

COC = combined oral contraceptive; LNG-IUS = levonorgestrel-releasing intrauterine system; MBL = menstrual blood loss; NS = not significant; PBLAC = pictorial blood assessment chart; TXA = tranexamic acid
[a]Crossover study.

Description of Results

Outcome Measures

All studies of NSAIDs examined bleeding outcomes. Eleven studies used the alkaline hematin method for an objective measure of MBL. Two trials used the pictorial blood loss assessment chart to assess blood loss.[63,77] One study[69] reported relief of menorrhagia for which methods were not provided.

Although we aimed to collect data on measures of quality of life, sexual function, fertility and time to conception, none of the 13 clinical trials reported on these outcomes. One study reported patient satisfaction based on participants' wish to continue treatment at the end of the study.[66]

MBL

Reduction Expressed as a Percent

Four trials of fair to good quality reported statistically significant reductions in MBL compared with baseline, ranging from 40 to 49 percent among those who received one to two treatment cycles of NSAIDs, including mefenamic acid, naproxen, or meclofenamate (Table 14).[67,72,75,76]

A good quality crossover trial conducted in the United States,[72] randomized 32 women with MBL more than 60 ml to meclofenamate or placebo for 2 treatment cycles. Seven (21%) participants were using an IUD. Significantly (p<0.0001) greater reductions in MBL were reported among those receiving meclofenamate (48.9 ± 3.7%) compared with those receiving placebo (9.2 ± 5.3%). During treatment, the change in MBL associated with meclofenamate ranged from −42 ± 3 percent in cycle 1 to −56 ± 8 percent in cycle 3.

A small, fair quality, RCT conducted in the Netherlands,[67] randomized women scheduled for a hysterectomy due to subjective menorrhagia to either mefenamic acid 500 mg (n=6) or placebo

(n=5) 3 times daily starting 5 days before expected menses to cessation of bleeding for 1 treatment cycle. Eligible participants had regular cycles, no IUD, and MBL more than 80 ml. Those receiving mefenamic acid had greater reductions (40%, p=0.01) in mean MBL from baseline compared with placebo where a nonsignificant increase (25%) in MBL was reported,

A randomized, double-blind crossover fair quality trial conducted in the United Kingdom[75] compared naproxen (550 mg at onset of menses then 275 mg every 6 to 8 hours for 5 days) to mefenamic acid among 38 women with MBL more than 80 ml for 2 treatment cycles. Patients with pelvic inflammation, fibroids, or other local disease were excluded. There were no significant differences in mean MBL reduction between the two groups receiving mefenamic acid (46% and 47%) and the two groups receiving naproxen (44% and 48%). Reductions in MBL compared with baseline were statistically significant (p<0.001) in both the groups receiving mefenamic acid and naproxen.

One crossover RCT of fair quality conducted in Australia and published in two papers[76,93] randomized 85 women with menorrhagia to mefenamic acid or placebo for two cycles. Overall there was a 28-percent reduction in mean MBL among those who received mefenamic acid compared with those who received placebo (p<0.001). There was a 30-percent reduction (p<0.001) in blood loss among those with MBL more than 80 ml at baseline (n=30) but a 28-percent increase in blood loss among those with MBL more than 35 ml at baseline (n=14).

Six poor quality trials also reported significantly reduced MBL compared with baseline levels (Table 14). One poor quality RCT conducted in the United Kingdom[63] compared 51 participants randomized to either mefenamic acid or to LNG-IUS. Both LNG-IUS and mefenamic acid significantly (p<0.005) reduced MBL compared with baseline; however, the study reported a greater reduction in median MBL among those treated with LNG-IUS (95%) compared with those receiving mefenamic acid (23%) after six cycles of treatment.

One RCT[66] conducted in Ireland randomized women to either TXA (n=27), mefenamic acid (n=25), or ethamsylate (n=29) for three cycles. The study reported a 54-percent reduction in mean MBL from baseline for those receiving TXA (p<0.001), a 20-percent reduction for those receiving mefenamic acid (p<0.001), and no reduction for those receiving ethamsylate.

A small crossover trial[71] conducted in Sweden compared TXA to flurbiprofen for two treatment cycles. A greater reduction in mean MBL from baseline was reported among those receiving TXA (53%) compared with those receiving flurbiprofen (24%).

One RCT conducted in the United Kingdom[70] examined the efficacy of mefenamic acid compared with norethisterone among 32 participants with MBL more than 80 ml for 2 cycles. Median percent change in blood loss volume was not significantly different between mefenamic acid (−24%; range, 5 to −83%) and norethisterone (−20%; range, 2 to −53%). Median MBL with treatment was 81 ml (range, 22 to 193 ml) for those receiving mefenamic acid and 92 ml (range, 43 to 189 ml) for those receiving norethisterone. One patient treated with mefenamic acid had an increase in blood loss.

One crossover trial[68] conducted in Australia examined the efficacy of mefenamic acid compared with low-dose COC (30 mcg ethinyl estradiol and 150 mcg levonorgestrel given daily for 21 days) in one group and mefenamic acid compared with naproxen in another group, each for two cycles among women with a clinical history of menorrhagia. There was no significant difference in reduction of mean MBL between those receiving mefenamic acid (38%) and those receiving low-dose COC (43%) or between those receiving mefenamic acid (20%) and those receiving naproxen (12%).

Table 14. Percent change in blood loss from baseline in studies of NSAIDs

Author, Year	NSAID	Comparator	NSAID Group	Comparator Group	NSAID vs. Comparator Group
Vargyas et al., 1987[72]	Meclofenamate	Placebo	−48.9	−9.2	p<0.0001
Van Elijkeren et al., 1992[67]	Mefenamic acid	Placebo	−40.0	NR	NR
Hall et al., 1987[75]	Mefenamic acid	Naproxen	−47.0	−46.0	NS
Fraser et al., 1981, 1984[76,93]	Mefenamic acid	Placebo	NR	NR	p<0.001
Reid and Virtanen-Kari,2005[63]	Mefenamic acid	LNG-IUS	−23.0	−95.0	p<0.001
Bonnar and Sheppard,1996[66]	Mefenamic acid	TXA	−20.0	−54.0	p<0.05
Bonnar and Sheppard,1996[66]	Mefenamic acid	Ethamsylate	−20.0	0	p<0.001
Fraser and McCarron, 1991[68]	Mefenamic acid	Naproxen	−20.0	−12.0	NS
Fraser and McCarron, 1991[68]	Mefenamic acid	COC[a]	−38.0	−43.0	NS
Cameron et al., 1990[70]	Mefenamic acid	Norethisterone	−24.0	−20.0	NS
Andersch et al., 1988[71]	Flurbiprofen	TXA	−24.0	−53.0	p<0.01

COC = combined oral contraceptive; LNG-IUS = levonorgestrel-releasing intrauterine system; TXA = tranexamic acid; NS = nonsignificant

[a]30 mcg ethinyl estradiol and 150 mcg levonorgestrel.

Reduction Expressed as a Volume

In four trials of fair to good quality,[67,72,75,76] treatment with meclofenamate, mefenamic acid or naproxen reduced MBL compared with baseline (Table 15). Mean or median MBL after treatment ranged from 65 to 77 ml. Mefenamic acid and naproxen were comparable in effectiveness.[75]

A good quality crossover trial conducted in the United States randomized 32 women to meclofenamate or placebo for 2 cycles. There was a significantly greater reduction in mean MBL from baseline with meclofenamate (72.6 ml) compared with placebo (6.0 ml).[72]

A small fair quality RCT conducted in the Netherlands randomized women scheduled for a hysterectomy due to subjective menorrhagia to mefenamic acid (n=6) or placebo (n=5). There was a significant reduction in mean MBL from baseline in the treatment group (43 ml, p=0.01) compared with a 38-ml increase in MBL in the placebo group.[67]

A fair quality crossover trial conducted in the United Kingdom compared naproxen to mefenamic acid among 38 women with MBL more than 80 ml for 2 treatment cycles. Median reductions in blood volume from baseline for mefenamic acid ranged from 54 ml to 61 ml (p<0.001) and the reduction for naproxen ranged from 52 to 62 ml (p<0.001) over 2 treatment cycles. There were no significant differences in reductions in MBL between mefenamic acid and naproxen.[75]

A fair quality crossover RCT conducted in Australia reported greater reductions in mean MBL among those receiving mefenamic acid (18.8 ml) for 2 treatment cycles compared with those receiving placebo. Among the women with MBL more than 80 ml at baseline (n=30), there was a significant ($p<0.001$) reduction in mean MBL (33.6 ml) among those receiving mefenamic acid compared with those receiving placebo.[76]

Six poor quality studies reported similar findings; NSAIDS significantly reduced MBL compared with baseline (Table 15). In a poor quality RCT conducted in the United Kingdom with 51 women,[63] MBL was reduced by 21 ml in those receiving mefenamic acid compared with baseline; however, the women in the LNG-IUS group reported significantly greater reductions in blood loss volume (117 ml, $p<0.001$) from baseline.

In an RCT conducted in Ireland,[66] 81 women were randomized to either TXA (n=27), mefenamic acid (n=25), or ethamsylate (n=29) for three cycles. Compared with baseline, those receiving TXA had an 89 ml reduction in MBL, those receiving mefenamic acid reported a 43 ml reduction, and those receiving ethamsylate reported an increase in MBL of 8 ml. Those receiving TXA had a 46 ml greater reduction in MBL compared with those receiving mefenamic acid ($p<0.05$) and those receiving mefenamic acid had a 51 ml greater reduction in MBL compared with those receiving ethamsylate; however, mean MBL (148 ml; range, 138 to 168 ml) after 3 cycles of treatment with mefenamic acid remained more than 80 ml.

In a crossover trial conducted in Australia, [68] there were no differences in absolute reductions in MBL volume between mefenamic acid and low-dose COC (30 mcg ethinyl estradiol and 150 mcg levonorgestrel given daily for 21 days) or between mefenamic acid compared with naproxen. Reductions in blood loss volume compared with baseline were reported for both those receiving mefenamic acid (38.1 ml, $p=0.002$) and those receiving COC (43.2 ml, $p<0.001$). In the other group, there were nonsignificant reductions in MBL from baseline for mefenamic acid (26 ml) and naproxen (15.5 ml).

In one RCT conducted in the United Kingdom,[70] median MBL was reduced after 2 cycles of mefenamic acid from 123 ml (range, 86 to 237 ml) to 81 ml (range, 22 to 193 ml), a reduction of 42 ml ($p<0.001$) and was significantly reduced with norethisterone from 109 ml (range, 81 to 236 ml) to 92 ml (range, 43 to 189 ml), a reduction of 17 ml ($p<0.002$), but there was no significant difference in reductions between mefenamic acid and norethisterone.

A small crossover trial[71] conducted in Sweden that compared TXA with flurbiprofen for two treatment cycles, reported significantly ($p<0.01$) greater reductions in mean MBL from baseline for TXA (140 ml, $p<0.01$) compared with the change in MBL from baseline for flurbiprofen (72 ml, $p<0.01$).

In another small RCT conducted in the United Kingdom,[74] median MBL was significantly reduced after two cycles of treatment with mefenamic acid (n=6), 38 ml reduction (median 47 ml; range, 39 to 210 ml) from baseline (85 ml; range, 68 to 169 ml), $p=0.05$, and was significantly reduced with a progesterone-impregnated intrauterine coil (n=7), 19 ml reduction (median 45 ml; range, 31 to 77 ml) from baseline (median 64 ml; range, 56 to 164 ml, $p<0.05$). However, there was no significant reduction in median MBL after two cycles of norethisterone (21 ml; median 110 ml; range, 18 to 187 ml).

Table 15. Change in blood loss volume from baseline in studies of NSAIDs

Author, Year	NSAID	Comparator	NSAID Group	Comparator Group	NSAID vs. Comparator Group
Vargyas et al., 1987[72]	Meclofenamate	Placebo	-72.6	-6.0	p<0.0001
Van Elijkeren et al., 1992[67]	Mefenamic acid	Placebo	-43.0	+38.0	NR
Hall et al., 1987[75]	Mefenamic acid	Naproxen	-57.5	-57.0	p=NS
Fraser et al., 1981, 1984[76]	Mefenamic acid	Placebo	NR	NR	p<0.001
Reid and Virtanen-Kari,2005[63]	Mefenamic acid	LNG-IUS	-21.0	-117.0	p<0.001
Bonnar and Sheppard,1996[66]	Mefenamic acid	TXA	-43.0	-89.0	p<0.05
Bonnar and Sheppard,1996[66]	Mefenamic acid	Ethamsylate	-43.0	+8.0	p<0.05
Fraser and McCarron, 1991[68]	Mefenamic acid	Naproxen	-26.0	-15.5	p=NS
Fraser and McCarron, 1991[68]	Mefenamic acid	COC[a]	-38.1	-43.2	p=NS
Cameron et al., 1990[70]	Mefenamic acid	Norethisterone	-42.0	-17.0	p=NS
Andersch et al., 1988[71]	Flurbiprofen	TXA	-72.0	-140.0	p<0.01
Cameron et al., 1987[74]	Mefenamic acid	Norethisterone	-38.0	-21.0	NR
Cameron et al., 1987[74]	Mefenamic acid	Progesterone-impregnated intrauterine coil	-38.0	-19.0	NR

COC = combined oral contraceptive; LNG-IUS = levonorgestrel-releasing intrauterine system; NSAID = nonsteroidal anti-inflammatory drug; NR = not reported; NS = nonsignificant

[a]Ethinyl estradiol (30 mcg)/levonorgestrel (150 mcg).

Pictorial Blood Loss Assessment Chart Score

One poor quality RCT conducted in India[77] randomized 110 women with menorrhagia to a combination of TXA and mefenamic acid or TXA alone for three treatment cycles. The pictorial blood loss assessment chart score was lowered by 146 points (59%, p<0.01) from baseline in those receiving mefenamic acid plus TXA and by 125 points (50%, p=NS) from baseline in those receiving TXA alone. In a poor quality RCT conducted in the United Kingdom,[63] women receiving mefenamic acid reported a 74-point reduction (p<0.001) in the median pictorial blood loss assessment chart score from baseline.

Relief of Menorrhagia

Improvement in the subjective relief of menorrhagia with NSAIDs was reported in two trials.[66,69] One RCT conducted in India[69] randomized 80 women with subjectively defined, cyclic, heavy bleeding to either mefenamic acid or placebo for three cycles. Relief of menorrhagia was significantly greater among those receiving mefenamic acid (86%) compared with those receiving placebo (20%). Another trial[66] reported that most women (57%) who

received mefenamic acid thought their blood loss was less after three treatment cycles compared with baseline. A small, placebo-controlled crossover trial conducted in Canada[73] randomized women to 2 cycles each of mefenamic acid and placebo and reported that 8 of the 10 women who competed the study experienced reductions in MBL during the mefenamic acid cycles compared with their placebo cycles ($p<0.05$).

Duration of Bleeding and Total Menstrual Fluid Loss

Duration of bleeding (in days) was reported in six trials of NSAIDs.[66,69,70,72,75,76] In two trials, one fair and one good quality, the duration of menstrual blood flow was shorter among those receiving either meclofenamate[72] or mefenamic acid[76] compared with placebo. Another fair quality study reported that both mefenamic acid and naproxen reduced the mean number of bleeding days.[75]

Two poor quality RCTs reported a significantly shorter duration of bleeding during mefenamic treatment cycles compared with pretreatment cycles,[69,70] but there was no change with norethisterone.[70] In one poor quality, three-arm trial[66] of mefenamic acid, TXA, and ethamsylate, there was no difference in duration of menstrual bleeding between treatment arms. In one poor quality study,[63] total menstrual fluid loss was significantly less at cycle 3 and cycle 6 compared with baseline among women receiving mefenamic acid.

Hemoglobin

In two trials,[71,72] hemoglobin concentrations did not increase during treatment with NSAIDs. In a good quality, crossover trial conducted in the United States, the median hemoglobin, hematocrit, and ferritin levels were unchanged compared with baseline.[72] In a crossover trial conducted in Sweden,[71] hemoglobin concentration during control cycles was no different from hemoglobin concentration during treatment. In the RCT in India,[77] mean hemoglobin increased significantly in the group receiving combined mefenamic acid and TXA (12.3 g/dl) and in the group receiving TXA alone (12.0 g/dl).

Head-to-Head Comparisons

Mefenamic Acid Versus Naproxen

Two crossover trials compared mefenamic acid to naproxen.[68,75] There were no differences in reduction of MBL between mefenamic acid and naproxen.

One fair quality crossover trial[75] conducted in the United Kingdom compared naproxen to mefenamic acid among 38 women with MBL more than 80 ml for 2 treatment cycles. Primary outcomes were mean MBL using the alkaline hematin method. Both mefenamic acid and naproxen reduced median MBL by 46 to 47 percent and 44 to 48 percent, respectively, compared with baseline. The median reductions in MBL volume from baseline for mefenamic acid ranged from 54 ml to 61 ml ($p<0.001$); the reduction for naproxen ranged from 52 to 62 ml ($p<0.001$) over two treatment cycles. There were no differences in reductions in MBL between mefenamic acid and naproxen.

One poor quality crossover trial[68] conducted in Australia randomized 30 women with a clinical history of menorrhagia to either mefenamic acid or naproxen for 2 cycles. The same dose of mefenamic acid was compared with oral contraceptives in a second group (see section below). The primary outcome was MBL measured by the alkaline hematin method. Mefenamic acid reduced mean MBL by 20 percent compared with baseline (p=NS). Naproxen reduced mean

MBL by 12 percent compared with baseline (p=NS) with no significant differences in reductions between mefenamic acid and naproxen. Despite these reductions, the majority of women receiving NSAIDs still had objective menorrhagia after treatment. There was considerable variability in response to both NSAIDs, with some women experiencing increases in MBL during treatment with NSAIDs.

Mefenamic Acid Versus Progesterone-Releasing Intrauterine Systems

Two poor quality RCTs conducted in the United Kingdom examined the efficacy of mefenamic acid compared with progesterone-releasing intrauterine systems. One studied the continuous LNG-IUS,[63] and the other studied an older progesterone-impregnated intrauterine coil that releases 65 mcg of progesterone daily.[74] Both trials used objective measures of MBL (alkaline hematin method) for inclusion criteria, but with slightly different volumes (more than 80 ml[63] and more than 50 ml[74]) to assess MBL outcomes.

One RCT with 51 participants[63] reported a statistically significant greater reduction in median MBL from baseline in the women with LNG-IUS (117 ml) compared with the women receiving mefenamic acid (21 ml) after six cycles of treatment. Significantly greater ($p<0.001$) reductions in the median pictorial blood loss assessment chart score and total menstrual fluid loss were also reported with LNG-IUS compared with mefenamic acid. Despite significant reductions with mefenamic acid, most patients still had objective MBL more than 80 ml.

One small RCT[74] reported reductions in median MBL after two cycles of treatment with both mefenamic acid (n=6), with a reduction of 21 ml (median 47 ml; range, 39 to 210 ml) from baseline (85 ml; range, 68 to 169 ml; p=0.05), and with the progesterone-impregnated intrauterine coil (n=7) with a reduction of 19 ml (median 45 ml; range, 31 to 77 ml) from baseline (median 64 ml; range, 56 to 164 ml; $p<0.05$). No statistics for head-to-head comparisons were reported.

NSAIDs Versus TXA

Two poor quality trials compared NSAIDs with TXA.[66,71] Both trials reported that women receiving TXA had significantly greater reductions in mean MBL compared with either mefenamic acid or flurbiprofen over three cycles.

One RCT[66] conducted in Ireland, randomized 81 women with MBL more than 80 ml to either TXA (n=27), mefenamic acid (n=25), or ethamsylate (n=29) for three cycles. There was a significant reduction in mean MBL from baseline over three treatment cycles for two of three treatment arms: 54 percent ($p<0.001$) for TXA and 20 percent ($p<0.001$) for mefenamic acid. The absolute change in MBL compared with baseline was −89 ml with TXA, −43 ml with mefenamic acid, and +8 ml with ethamsylate.

One small randomized crossover trial[71] conducted in Sweden compared TXA to flurbiprofen in 15 women with MBL more than 80 ml. The trial reported a statistically significant reduction in mean MBL (53%) in the group receiving TXA (53%) compared with the group receiving flurbiprofen (24%). Absolute reductions in blood loss volume from baseline were greater for TXA (140 ml) compared with flurbiprofen (72 ml).

TXA Plus Mefenamic Acid Versus TXA Alone

One poor quality RCT conducted in India[77] randomized 110 women with menorrhagia (not objectively defined) to a combination of TXA and mefenamic acid or to TXA alone. After three treatment cycles, the pictorial blood loss assessment chart score was reduced in those receiving

mefenamic acid plus TXA (59%, p<0.01) and in those receiving TXA alone (50%, p=NS). No statistics for head-to-head comparisons were reported.

Mefenamic Acid Versus Norethisterone

Two poor quality RCTs conducted in the United Kingdom examined the efficacy of mefenamic acid compared with norethisterone. [70,74] Both trials examined the same dose and duration of mefenamic acid (500 mg 3 times daily on cycle days 1 to 5) and the same dose of norethisterone (5 mg twice per day) but given during slightly different cycle days, (days 19 to 26[70] vs. days 15 to 25[74]). Both trials used the alkaline method for MBL measurement for inclusion (50 to 80 ml) and outcome criteria.

One RCT[70] reported no difference in reductions of median MBL among those receiving 2 treatment cycles of mefenamic acid (n=17) compared with those receiving norethisterone (n=15). With either treatment, the majority of women still had MBL more than 80 ml. In the other small RCT,[74] no statistics for head-to-head comparisons were reported. Compared with baseline, median MBL was reduced after treatment with mefenamic acid (n=6) by 38 ml and by 21 ml (p=NS) among those receiving norethisterone (n=6). Median MBL with treatment was 47 ml (range, 39 to 210 ml) with mefenamic acid and 110 ml (range, 24 to 222 ml) with norethisterone.

Mefenamic Acid Versus Low-Dose COC

One poor quality crossover trial[68] conducted in Australia examined the efficacy of mefenamic acid compared with low-dose COC with 30 mcg ethinyl estradiol and 150 mcg levonorgestrel given daily for 21 days among 30 women with a clinical history of menorrhagia. There were no differences between mefenamic acid and COC in reductions in mean MBL (38% vs. 43%) or absolute reductions in MBL volume (38 ml vs. 43 ml).

Tranexamic Acid

Key Points

- Women taking TXA at a dose of 1.95 to 4.5 grams per day for 4 to 5 days from the onset of bleeding experienced a clinically significant reduction in MBL, ranging from 26 percent to 54 percent in studies lasting up to 1 year. However, there are no long-term followup studies.
- In comparison to progestogens, combined hormonal pills, and NSAIDs, TXA appeared to provide greater reduction in MBL. No head-to-head comparisons of TXA versus LNG-IUS were assessed.
- The number of reports of side-effects and adverse effects was generally not significantly different between TXA and the comparator.
- Although no thromboembolic events were reported in any of the included TXA studies, there are concerns about the possible increased risk of thromboembolic events in particular women. The Food and Drug Administration (FDA) has issued precautions and contra-indications.

Detailed Synthesis

TXA is a competitive inhibitor of plasminogen activation, thereby acting as an antifibrinolytic agent. TXA does not appear to affect platelet numbers or aggregation but acts to reduce the breakdown of fibrin in a preformed clot. Because menstrual bleeding involves

liquefaction of clotted blood from the spiral endometrial arterioles, a reduction in this process is the putative mechanism of reduced menstrual bleeding.

Seven RCTs of TXA were identified (Table 16).[66,71,77-81] One study compared TXA alone to TXA plus mefenamic acid, and is discussed in the NSAIDs section above.[77] For the six other studies of TXA, study population ranged from 15[71] to 304.[81] The total number of women randomized to TXA was 475. The total number of women assigned to TXA for whom study endpoint outcome measures were collected, including intention to treat missing data protocols, was 460.

For five of the trials, the bleeding criterion for study entry was a mean MBL (assessed using the alkaline hematin method) of at least 80 ml for two or three cycles prior to randomization.[66,71,78,80,81] A sixth trial used the pictorial blood loss assessment chart score greater than 100 to enroll participants.[79] The mean MBL at baseline was similar for four of the trials (range, 153 to 186 ml).[66,78,80,81] The mean MBL at baseline was 295 ml for one trial.[71]

The intervention dosage differed among the six trials. The TXA administration protocols for each menstrual cycle were: 1.95 grams per day or 3.9 grams per day for up to 5 days,[81] 2 grams per day for 5 days,[79] 3.9 grams per day for up to 5 days,[78] 4 grams per day for 4 days,[80] 4 grams per day for 5 days,[66] 4.5 grams per day for 3 days and then 2 grams per day for 2 days.[71]

Two of the studies were placebo-controlled.[78,81]The comparator differed across the other four trials and included: oral MPA for 20 days,[79] oral norethisterone for 7 days,[80] mefenamic acid for 5 days,[66] ethamsylate for 5 days,[66] and flurbiprofen for 5 days.[71]

The primary outcome of the trials was change in blood loss (absolute volume or percent) or change in pictorial blood loss assessment chart score. The alkaline hematin method was used to assess MBL in five trials.[66,71,78,80,81] The absolute change in mean blood loss from baseline and percent change were reported in five studies.[66,71,78,80,81] Three of these four reported mean MBL,[71,78,80] and three reported median MBL.[66,78,80] One trial used the pictorial blood loss assessment chart, which is a validated chart that helps participants more uniformly report bleeding as represented by the degree of saturation of sanitary pads and tampons, for the outcome measure.[79]

The timing of the summative outcome measure reporting varied among the trials. Two trials reported after two menstrual cycles.[71,80] Two trials reported after three menstrual cycles.[66,81] Two trials reported after six menstrual cycles.[78,79]

The setting varied: two trials were conducted in the United States,[78,81] three in Europe,[66,71,80] and one in India.[79] Overall one study was assessed as good quality,[78] two were fair quality,[80,81] and three were poor quality.[66,71,79] Details of quality scoring for individual publications are included in Appendix I.

Table 16. Primary outcomes of TXA for abnormal cyclic uterine bleeding

Author, Year Country Quality	Comparison Groups (n)	Key Outcomes
Lukes et al., 2010[78] United States Good	**G1:** TXA 1.3 g 3 times daily up to 5 days per cycle (123) **G2:** Placebo (73)	• Mean reduction in MBL measured by the alkaline hematin method after 6 cycles was greater in G1 compared with G2 (p<0.001). • Proportion of women with at least 50 ml reduction in MBL was 56% in G1 and 19% in G2 (p<0.0001). • Women in G1 reported improvements in quality of life (measured by the Menorrhagia Impact Score) compared with G2 (p<0.01).
Freeman et al., 2011[81] Fair	**G1:** TXA 3.9 g per day for up to 5 days of menstrual bleeding (118) **G2:** TXA 1.95 g per day for up to 5 days of menstrual bleeding (117) **G3:** Placebo (69)	• Mean MBL was significantly reduced during treatment compared with baseline for G1 (26%) and for G2 (39%). • The reduction in mean MBL was significantly greater in the group receiving the higher TXA dose (G2).
Preston et al., 1995[80] United Kingdom Fair	**G1:** TXA 1 g 4 times daily for 4 days (25) **G2:** Norethisterone 5 mg twice a day on days 19 to 26 (21)	• Mean reduction in MBL from baseline was 45% for G1 (p<0.0001); mean MBL increased in G2 (p=NS). • Fourteen (56%) women in G1 and 2 (9.5%) women in G2 achieved MBL<80 ml.
Kriplani et al., 2006[79] India Poor	**G1:** TXA 500 mg 4 times daily for 5 days (50) **G2:** MPA 10 mg twice daily days 5 to 25 (50)	• Both groups had significant (p<0.005) reductions in PBLAC scores after 3 months and mean reduction in blood loss was 60.3% in G1 and 57.7% in G2. • Hemoglobin levels rose in both groups (p<0.05 for both). • Three women in G1 (6.1%) and 13 (28.9%) in G2 did not respond to treatment (p=0.003).
Bonnar and Shepard, 1996[66] Ireland Poor	**G1:** TXA 1 g every 6 hrs. (27) **G2:** Ethamsylate 500 mg every 6 hrs. (29) **G3:** Mefenamic acid 500 mg every 8 hrs. (25)	• Women in G1 had blood loss reduction of 54% compared with 20% for women in G3. • No reduction in blood loss for G2.
Andersch et al., 1988[71] Sweden Poor	**G1:** TXA for 2 cycles followed by flurbiprofen for 2 cycles (15)[a] **G2:** Flurbiprofen for 2 cycles followed by TXA for 2 cycles (15)[a]	• MBL was significantly reduced during treatment with flurbiprofen and TXA. • MBL was significantly (p<0.01) lower during treatment with TXA compared with flurbiprofen.

MBL = menstrual blood loss; PBLAC = pictorial blood assessment chart
[a]Crossover study.

Description of Results

Outcome Measures

The alkaline hematin method for MBL was used as an outcome measure in 5 of the TXA trials.[66,71,78,80,81] One poor quality trial used the pictorial blood loss assessment chart to assess blood loss, with menorrhagia defined by a pictorial blood loss assessment chart score of 100 or greater.[79] Other outcome measures included hemoglobin level, treatment success, and quality of life.

MBL

Reduction Expressed as a Percent

In five studies (one good quality, two fair quality, and two poor quality), TXA was associated with significant reductions in MBL ranging from 26 to 54 percent (Table 17). A good quality placebo-controlled trial reported a statistically significant ($p<0.001$) reduction in mean MBL among women in the modified intent-to-treat population receiving TXA (40%) compared with those receiving placebo (8%) for six menstrual cycles. The attributable reduction for TXA was 32 percent ($p<0.001$).[78] The other placebo-controlled trial of fair quality reported significant reductions in mean MBL for women receiving 3.9 or 1.95 grams per day of TXA (39% and 26%, respectively) compared with a reduction in MBL of 2 percent for women taking placebo ($p<0.001$).[81]

The trial that compared TXA with norethisterone reported a statistically significant reduction in mean MBL among women receiving TXA for two treatment cycles compared with those receiving norethisterone: 45-percent reduction (95% CI, 23% increase to 93% reduction; $p<0.0001$ vs. baseline) compared with a 20-percent increase (95% CI, 114% increase to 62% reduction; $p=0.26$ vs. baseline).[80]

A trial that compared TXA with ethamsylate and with mefenamic acid reported that over three treatment cycles the mean reduction in MBL from baseline for the group receiving TXA was 54 percent ($p<0.001$). For the mefenamic acid group the mean reduction in MBL from baseline was 20 percent ($p<0.001$). There was no change in MBL for the ethamsylate group.[66]

A small, poor quality, crossover trial (n=15) that compared TXA with flurbiprofen reported that over two treatment cycles the mean reduction in MBL from baseline for TXA was 53 percent ($p<0.01$) compared with 24 percent for flurbiprofen ($p<0.01$).[71]

Table 17. Percent change in blood loss from baseline in studies of TXA

Author, Year	Comparator	TXA Group	Comparator Group	TXA vs. Comparator Group
Lukes et al., 2010[78]	Placebo	-40.4	-8.2	p<0.001
Freeman et al., 2011[81]	Placebo	-38.6 (high dose) -26.1 (low dose)	-1.9	p<0.0001
Preston et al., 1995[80]	Norethisterone	-45.0	+20.0	p<0.0001
Bonnar and Shepard, 1996[66]	Mefenamic acid	-54.0	-20.0	p<0.05
Bonnar and Shepard, 1996[66]	Ethamsylate	-54.0	Increased	p<0.0001
Andersch et al., 1988[71]	Flurbiprofen	-53.0	-24.0	p<0.01

MPA = medroxyprogesterone; NS = nonsignificant; NR = not reported

Reduction Expressed as a Volume

In five studies (one good quality, two fair quality, and two poor quality) TXA was associated with significant reductions in MBL ranging from 47 to 140 ml (Table 18). Both placebo-controlled trials reported a statistically significant reduction in mean MBL for women treated with TXA.[78,81] Among women in the modified intent-to-treat population receiving TXA for six menstrual cycles, one study reported a reduction in MBL of 69.6 ml compared with a reduction

of 12.6 ml in the placebo group; the attributable reduction for TXA was 57 ml (p<0.001). The calculated least-squares mean reduction in MBL in the modified intent-to-treat population receiving TXA (66.3 ml) was greater compared with those receiving placebo (17.8 ml); the attributable reduction for TXA was 48.5 ml (p<0.001).[78] The effect size for TXA (standardized observed effect) was 0.67 based upon the modified intention to treat analysis and the standard deviation. The effect size was 0.49 based upon the least squares mean change analysis and the standard deviation.[78] The effect size for TXA compared with placebo is large.

In the larger fair quality study that compared high-dose (3.9 g/day) and low-dose (1.95 g/day) TXA to placebo, the mean reduction from baseline for the intent-to-treat population was 65.3 ml and 46.5 ml, respectively, while the placebo group had a small insignificant decline of 3.0 ml. The low-dose group did not meet the authors predetermined threshold of at least 50 ml per cycle reduction in MBL from baseline, but both groups treated with TXA did achieve a reduction in MBL from baseline that exceeded the threshold determined by authors to be meaningful to women (36 ml/cycle).[81]

A small fair quality trial that compared TXA with norethisterone reported a statistically significant reduction in mean MBL occurred among women receiving TXA for two treatment cycles compared with those receiving norethisterone: 79 ml reduction (95% CI, 62 to 108 ml reduction) compared with 34 ml increase (95% CI, −2 to 64 ml reduction).[80]

A trial that compared TXA with ethamsylate and with mefenamic acid reported that the pretreatment MBL in the TXA group ranged from 143 to 178 ml, and over three treatment cycles the mean MBL was 72 to 77 ml, a mean reduction in MBL of 89 ml (range, 24 to 214 ml, p<0.001). For the ethamsylate group, the pretreatment MBL ranged from 157 to 185 ml, and over three treatment cycles the mean MBL was 161 to 185 ml, a mean increase of 8 ml (range, 280 to 103 ml). For the mefenamic acid group, the pretreatment MBL ranged from 159 to 199 ml, and over three treatment cycles the mean MBL was 138 to 168 ml, a mean reduction in MBL of 43 ml (range, 82 to 179 ml; p<0.001).[66] Head-to-head comparisons of the results of treatment on absolute changes in blood loss showed that TXA reduced the mean loss by 97 ml more than with ethamsylate (95% CI, 54 to 140 ml, p<0.001) and by 56 ml more than with mefenamic acid (95% CI, 2 to 90 ml, p<0.05).[66]

A small crossover trial that compared TXA with flurbiprofen reported that over two treatment cycles the mean reduction in MBL from baseline for TXA was 140 ml (SD ± 33 ml, p<0.01), compared with 72 ml (SD ± 44 ml, p<0.01) for flurbiprofen.[71]

Table 18. Change in blood loss volume from baseline in studies of TXA

Author, Year	Comparator	TXA Group	Comparator Group	TXA vs. Comparator Group
Lukes et al., 2010[78]	Placebo	−69.6 ml	−12.6 ml	p<0.001
Freeman et al., 2011[81]	Placebo	-65.3 ml (high-dose) -46.5 ml (low-dose)	-3.0 ml	p<0.0001
Preston et al., 1995[80]	Norethisterone	−79.0 ml	+34.0 ml	p<0.0001
Bonnar and Shepard, 1996[66]	Mefenamic acid	−89.0 ml	−43.0 ml	p<0.05
Bonnar and Shepard, 1996[66]	Ethamsylate	−89.0 ml	+8.0 ml	p<0.001
Andersch et al., 1988[71]	Flurbiprofen	−140.0 ml	−72.0 ml	p<0.01

NR = not reported

Pictorial Blood Loss Assessment Chart Score

One poor quality trial that used the pictorial blood loss assessment chart score as the blood loss measure, compared TXA with oral MPA and reported a significant ($p<0.005$) reduction in the pictorial blood loss assessment chart score over three treatment cycles from baseline for both TXA (60.3%) and MPA (57.7%).[79]

Hemoglobin

Four studies[71,78-80] reported changes in hemoglobin level. In the good quality study, mean hemoglobin levels were unchanged from baseline for women taking TXA (0.02 ± 1.10 g/dL) while the placebo group had a statistically significant increase (0.34 ± 0.66 g/dL) that was not considered clinically significant.[78] The post treatment hemoglobin levels were similar (estimated difference 0.2 g/dl, 95% CI, −0.5 to 0.9) in the TXA (12.9 g/dl) and norethisterone groups (12.6 g/dl).[80] Hemoglobin levels rose significantly from baseline for women taking TXA ($p=0.0003$) and women taking MPA ($p=0.02$).[79] The small crossover trial did not find differences in mean hemoglobin during the control cycles (127.4 ± 3.7 g/l) compared with either TXA (126.2 ± 3.0 g/l) or flurbiprofen (127.2 ± 3.4 g/l) cycles.[71]

Treatment Success

One placebo-controlled trial reported a statistically significant difference ($p<0.001$) for achieving a MBL below 80 ml (standard definition of heavy menstrual bleeding) in the modified intent-to-treat population between women receiving TXA (43%) compared with those receiving placebo (17%) for six menstrual cycles.[78] This same study reported that 69 percent of cycles in the TXA group achieved a predetermined MBL reduction of at least 36 ml, representing a blood loss reduction considered meaningful to women.[78] In the three-arm placebo controlled study, women receiving the higher (3.9 g/day) and lower (1.95 g/d) dose of TXA achieved a reduction in MBL from baseline that was perceived as meaningful to participants; however, only participants receiving the higher dose of TXA (3.9 g/day) achieved a mean reduction in MBL that exceeded 50 ml per cycle.[81]

Quality of Life

One placebo-controlled trial reported a statistically significant ($p<0.001$) difference in social or leisure activities, and in physical activity, favoring TXA.[78] Women taking TXA has significant improvements in quality of life as assessed by the Menorrhagia Impact Questionnaire.[81]

Head-to-Head Comparisons

TXA Versus Norethisterone and MPA

The trial that compared TXA with norethisterone reported a statistically significant ($p<0.0001$) reduction in mean MBL for women receiving TXA for two treatment cycles compared with no reduction for women receiving norethisterone.[80] Expressed as percentage, the change in MBL for TXA was a 45-percent reduction (95% CI, 23% increase to 93% reduction; $p<0.0001$ vs. baseline) compared with an increase of 20 percent (95% CI, 114% increase to 62% reduction; $p=0.26$ vs. baseline) for norethisterone; expressed as a measure of volume, there was a reduction in MBL of 79 ml (95% CI, 62 to 108 ml reduction) for TXA compared with an increase of 34 ml (95% CI, −2 to 64 ml reduction) for noresthisterone.[80]

In a trial that compared TXA with oral MPA, both groups experienced significant reductions in MBL compared with baseline; the effect of these interventions was comparable (p=0.78). [79]

TXA Versus Mefenamic Acid, Ethamsylate, and Flurbiprofen,

TXA reduced the mean blood loss by 97 ml more than with ethamsylate (95% CI, 140 to 54, p<0.001) and by 46 ml more than with mefenamic acid (95% CI, 90 to 2 ml, p<0.05).[66] The trial that compared TXA with flurbiprofen reported that the reduction in MBL during treatment with TXA was significantly (p<0.01) greater than the reduction reported during treatment with flurbiprofen.[71]

Combined Oral Contraceptives

Key Points

- In two medium-sized RCTs, treatment of affected women with estradiol valerate and dienogest led to improvement in a range of AUB symptoms, including both overall complete response and effects on relevant laboratory values (e.g., hemoglobin, ferritin).
- In one small RCT and one small randomized crossover study of combination therapy with ethinyl estradiol and levonorgestrel and one small RCT assessing therapy with ethinyl estradiol and norethindrone acetate, COC treatment was associated with significant reductions in MBL as compared with baseline.

Detailed Synthesis

We identified five RCTs that explored the effects of therapy with COCs on the incidence and severity of abnormal cyclic uterine bleeding including two studies examining estradiol valerate and dienogest,[82,83] two studies examining ethinyl estradiol plus levonorgestrel,[59,68] and one study examining the combination of norethindrone acetate and ethinyl estradiol (Table 19).[61] All five studies were industry-sponsored.[59,61,68,82,83] Three were multicenter RCTs, involving Australia and Europe,[82] the United States and Canada,[83] and Canada,[61] and two were academic single center studies, one conducted in Egypt[59] and one conducted in Australia.[68] Two of the studies included seven 28-day cycles of therapy with the primary response rate determined after 90 days of therapy,[82,83] while one examined outcomes after 6 months[68] and two assessed outcomes after 12 months.[59,61] Two studies employed a placebo comparison group,[82,83] two compared COCs to LNG-IUS,[59,61] and one included a randomized crossover comparison of a COC to mefenamic acid.[68]

Table 19. Primary outcomes of COCs for abnormal cyclic uterine bleeding

Author, Year Country Quality	Comparison Groups (n)	Key Outcomes
Fraser et al., 2011[82] United States, Canada Good	**G1:** Estradiol valerate and dienogest (149) **G2:** Placebo (82)	• Full resolution of qualifying abnormal menstrual symptoms during the first 90 days of treatment observed in 40.7% of G1, as compared with 1.6% of G2 (p<0.0001). • Mean reduction in MBL was 69% in G1 vs. 5.8% in G2 and there were significant reductions in days of bleeding (p=0.0186), and number of sanitary protection items used (p<0.0001) observed in G1 vs. G2. • G1 participants had significant improvements vs. baseline in hemoglobin, hematocrit, and ferritin values; no similar change in G2.
Jensen et al., 2011[83] Australia, Europe Good	**G1:** Estradiol valerate and dienogest (120) **G2:** Placebo (70)	• Full resolution of qualifying abnormal menstrual symptoms during the first 90 days of treatment observed in 43.8% of G1 vs. 4.2% of G2 (p<0.001). • Mean reduction in MBL was 353 ml (64.2%) in G1 vs. 130 ml (18.7%) in G2 (p<0.001). • G1 participants had significant improvements vs. baseline in hemoglobin, hematocrit, and ferritin values; no similar change in G2.
Shaaban et al., 2011[59] Egypt Poor	**G1:** LNG-IUS (56) **G2:** Ethinyl estradiol and levonorgestrel (56)	• G2 associated with significant reduction in MBL at 12 months vs. baseline from 274.3 ± 142.6 ml to 118.2 ± 75.0 ml (p<0.001). • Reduction in MBL at 12 months was significantly greater in the G1 vs. G2. • Significant improvements in patient assessment of overall health noted in G1 and G2.
Endrikat et al., 2009[61] Canada Poor	**G1:** LNG-IUS (20) **G2:** Ethinyl estradiol and norethindrone acetate (19)	• G1 and G2 experienced a significant decreased in MBL at 12 months compared with baseline. Mean decrease of 68% in MBL for G2 (p<0.001). • Median MBL in G2 decreased from 290 ml at baseline to 72 ml at 12 months.
Fraser et al., 1991[68] Australia Poor	**G1:** Mefenamic acid (12)[a] **G2:** Ethinyl estradiol and levonorgestrel (12)[a]	• Significant reduction in mean MBL observed during the COC treatment cycles (43%) as compared with baseline. (p<0.001). • At least 20% reduction in MBL as compared with the preceding baseline cycles was observed in 10/12 patients during mefenamic acid treatment and 9/12 during COC treatment.

LNG-IUS = levonorgestrel-releasing intrauterine system; MBL = menstrual blood loss; COC = combined oral contraceptive
[a]Crossover study.

All studies assessed measures related to changes in MBL, including use of the alkaline hematin method[59,68,82,83] and the pictorial blood loss assessment chart.[59,61] Other outcomes included number of sanitary items used, a composite outcome of menstrual bleeding-related factors,[82,83] and related hematologic parameters (i.e., hematocrit, hemoglobin, and/or serum ferritin).[59,61,82,83] One study also assessed potential impact on health-related quality of life[15] and one described effects on a menorrhagia symptom severity score.[61] None of the studies assessed any potential effect modifiers.

Among the five studies of COC therapy, two were good quality[82,83] and three were poor quality.[59,61,68] Details of quality scoring for individual publications are included in Appendix I.

Description of Results

Estradiol Valerate and Dienogest

Two multicenter RCTs with the same industry sponsor assessed the utility of estradiol valerate and dienogest in treatment of women with AUB, defined as prolonged, frequent, and/or heavy bleeding. The first RCT[82] was conducted in Australia and Europe and comprised 231 women, randomized at a 2:1 ratio after a 90-day run-in period to receive estradiol valerate and dienogest for seven 28-day cycles. The study drug regimen included estradiol valerate 3 mg on days 1 to 2, estradiol valerate 2 mg and dienogest 2 mg on days 3 to 7, estradiol valerate 2 mg and dienogest 3 mg on days 8 to 24, estradiol valerate 2 mg on days 25 to 26, and placebo on days 27 to 28. Complete response, defined as full resolution of qualifying abnormal menstrual symptoms during the first 90 days of treatment as compared with the 90-day run-in phase, was observed in 29.5 percent of the estradiol valerate and dienogest group, as compared with 1.2 percent of the placebo-treated patients ($p<0.0001$). Treatment with estradiol valerate and dienogest was also associated with significant reductions in volume of MBL ($p<0.0001$), days of bleeding ($p=0.02$), and number of sanitary protection items used ($p<0.0001$) as compared with the placebo group. The estradiol valerate and dienogest-treated patients also experienced significant improvements versus baseline in hemoglobin, hematocrit, and ferritin values; similar improvements were not observed in the placebo-treated group.

The second RCT[83] was conducted at centers in the United States and Canada, employing the same dose and randomization schema and including 190 women with AUB. Complete response, defined as full resolution of qualifying abnormal menstrual symptoms during the first 90 days of treatment as compared with the 90-day run-in phase, was observed in a significantly greater proportion of the estradiol valerate and dienogest group (35/80, 44%) as compared with the placebo group (2/48, 4%, $p<0.001$). The mean reduction in MBL was also greater in the estradiol valerate and dienogest (−353 ml or −64% vs. loss during run-in phase) when compared with the placebo group (−130 ml or −19% vs. observed run-in loss, $p<0.001$). Individuals in the estradiol valerate and dienogest group also experienced significant improvements in hemoglobin, hematocrit, and ferritin values as compared with the run-in phase, while similar improvements were not observed in the placebo group.

Ethinyl Estradiol and Levonorgestrel

Two randomized controlled trials assessed the utility of an ethinyl estradiol (30 mcg) and levonorgestrel (150 mcg) combination in women with menorrhagia.[59,68] One of these trials was a single center RCT involving 112 women with idiopathic menorrhagia randomized to LNG-IUS (n=56) or ethinyl estradiol/levonorgestrel (n=56) for 12 months.[59] Efficacy data from the LNG-IUS arm of the study is discussed further in the LNG-IUS section of this report. In this trial, the COC regimen was associated with a significant reduction in MBL as assessed by the alkaline hematin method at 12 months as compared with baseline, from 274.3 ± 142.6 ml to 118.2 ± 75.0 ml ($p<0.001$); however, the overall reduction in MBL was significantly greater in the LNG-IUS group as compared with the COC group. Significant improvements in patient assessment of overall health and reduction in physically ill days were noted in both treatment groups.

The other trial assessing the use of ethinyl estradiol and levonorgestrel was a crossover study in women with menorrhagia, with one arm comparing outcomes of 12 women treated sequentially with mefenamic acid (500 mg every 12 hours from first sign of menses until 24 hours after usual duration of heavy bleeding) and COCs for two cycles each in random order,

with a two-cycle washout period between treatment cycles.[68] Additional efficacy details for mefenamic acid and for another treatment arm in this study involving naproxen are further discussed in the NSAIDs section of this report. A significant ($p<0.001$) reduction in mean MBL as measured by the alkaline hematin method was observed during the COC treatment cycles as compared with baseline (43%); the reduction in mean MBL during the mefenamic acid treatment period was not significantly different than the COC treatment period. A response of at least 20 percent reduction in MBL as compared with the preceding baseline cycles was observed in 10 of 12 patients during mefenamic acid treatment and in 9 of 12 during COC treatment. One patient responded to COCs but not to mefenamic acid, and two patients exhibited a response to mefenamic acid but not to the COC regimen.

Ethinyl Estradiol and Norethindrone Acetate

One multicenter randomized controlled trial compared the combination of ethinyl estradiol (20 mcg) and norethindrone acetate (1 mg) to use of a levonorgestrel-releasing intrauterine system (LNG-IUS) over 12 months in 39 women with idiopathic menorrhagia.[61] Efficacy data from the LNG-IUS arm of the study is also discussed further in the levonorgestrel-releasing intrauterine system section of this report. The LNG-IUS arm included 17 women and the COC arm included 12. Both arms experienced a significant ($p<0.001$) decrease in MBL at 12 months as compared with baseline, with a decrease from a median MBL of 290 ml at baseline to a median of 72 ml at 12 months observed in the COC group (mean decrease 68%). The decrease in MBL, however, was significantly greater in the LNG-IUS group versus the COC group ($p=0.002$). Treatment success, defined as MBL less than 100 at 12 months, was observed in a significantly ($p<0.009$) greater proportion of the LNG-IUS participants (80%) as compared with the COC group (37%). Menorrhagia symptom severity scores were also significantly lower in the LNG-IUS group at 6 months as compared with the COC group ($p=0.05$). No significant changes in hemoglobin concentration were observed in either group during the study.

Use of Decision Aids in Treatment of Menorrhagia

Key Points

- Three RCTs evaluated decision aids to assist patients with menorrhagia. All were of poor quality due to lack of blinding of participants and care providers.
- Improvements in general health status, the primary outcome for 2 studies, were not associated with decision aids. One study reported lower use of hysterectomy among women who had an interview prior to their consultation while another study did not show differences in hysterectomy rates after 1 year. Two studies did not report differences in treatment outcomes after 6 months or 1 year.

Detailed Synthesis

Decision aids are interventions to inform patients of their treatment options when more than one option exists. A recent Cochrane review of RCTs of decision aid[94] found that decision aids are beneficial in increasing patient knowledge of treatment options, help to clarify benefits and harms associated with therapeutic choices, and increase patient participation in decision selection. They have been shown to reduce elective surgery and have no apparent adverse effects on patient outcomes or satisfaction.[94]

We identified three RCTs with four publications[85-87,95] about medical decision aids in women with menorrhagia (Table 20). All of the studies used a written decision aid booklet; one study evaluated a computerized decision aid in conjunction with the pamphlet and one study also mailed participants a videotape and conducted an interview prior to clinical appointment. Diagnosis of menorrhagia was determined from medical records and not quantified in any of the studies. Length of followup ranged from 6 months to 2 years. Two studies were conducted in the United Kingdom[86,87] and one was conducted in Finland.[85] These studies were all of poor quality.

The largest study (n=894), conducted in England, randomized women to receive booklet and videotape with interview, materials without interview, or standard practice groups.[86] General health status improved significantly and menorrhagia severity decreased in all three groups. Treatment rates were similar in all groups after 2 years. Women in the interview group had a lower rate of hysterectomy and reported greater satisfaction with treatment results. A medium sized Finnish study evaluated the effectiveness of a mailed information booklet on treatment outcomes and general health status after 1 year.[85,95] More women who received the decision aid were less likely to receive newer treatment methods including minor surgery or LNG-IUS (16% vs. 26%, p=0.03). Most of the measured health outcome scores improved after 1 year for both groups with no significant difference in patient satisfaction, knowledge, anxiety or sexual satisfaction.

A small English study[87] conducted from 2003 to 2005 evaluated a computerized decision aid in conjunction with a patient leaflet. Women in the intervention group had significantly less decisional conflict at 2 weeks and higher knowledge scores at 6 months. There were no significant group differences in anxiety or treatments received after 6 months.

Although decision aids do help to increase patient knowledge, there are some methodological limitations in these studies, including low participation rates, large number of drop outs, and lack of blinding. The diagnosis of menorrhagia was not quantified and no effect modifiers were examined in any of these studies. Information on harms was not reported in any of the decision aid studies.

Table 20. Primary outcomes of decision aids for abnormal cyclic uterine bleeding

Author, Year Country Quality	Comparison Groups (n)	Outcomes	Results
Protheroe et al., 2007[87] United Kingdom Poor	**G1:** Computerized decision aid and information leaflet (74) **G2:** Information leaflet only (72)	**Primary:** total score on Decisional Conflict Scale **Secondary:** anxiety, quality of life, knowledge, treatment preferences	• Decisional conflict was significantly reduced in G1 vs. G2 (adjusted difference 16.6 95% CI, 21.5 to 11.6, p<0.001). • Anxiety declined slightly for both groups (p=NS). • Quality of life and knowledge scores improved in both groups but more in G1 as compared with G2.
Vuorma et al., 2004[85,95] Finland Poor	**G1:** Information booklet (184) **G2:** Usual care (179)	**Primary:** Planned treatment at 3 months and actual treatment at 1 year General health status measured by RAND -36 **Secondary:** knowledge of treatment methods, satisfaction with communication anxiety and sexuality	• Fewer women in G1 received newer treatments (minor surgery or LNG-IUS) (p=0.03); hysterectomy rates were similar in both groups. • Most health status measures improved for both groups. • At 3 months 18% of women in G1 and 8% in G2 had received prescription for oral medication (p=0.007). • There were no differences between groups in anxiety, satisfaction, knowledge or sexual satisfaction.
Kennedy et al., 2002[86] United Kingdom Poor	**G1:** Interview and information booklet (300) **G2:** Information booklet only (296) **G3:** No intervention (298)	**Primary:** general health status measured using SF-36 **Secondary:** treatments received during followup, severity of menorrhagia, patient satisfaction	• Health status measures improved for all 3 groups. Treatment rate (81%) during study was similar for all 3 groups (p=0.17) but women in G1 were less likely to have a hysterectomy (OR 0.60 95% CI, 0.38 to 0.96). • G1 were more satisfied in taking part in treatment decision and with results compared with G3.

CI = confidence interval; OR = odds ratio; NS = nonsignificant

KQ2. Harms of Interventions for Management of Abnormal Bleeding

Description of Included Studies and Sources of Information

Capturing useful information about potential harms of treatment for reproductive-age women that is specifically applicable to interventions for abnormal bleeding is a challenge. A wide range of interventions are used to treat abnormal bleeding. Twelve interventions relevant to the primary care setting were identified for this report. They range from medications that are exceptionally familiar to providers such as NSAIDs to potentially less familiar or newer medications like exenatide (an injectable diabetes agent). Interventions also include those with widespread use and many indications, like oral contraceptive pills or acupuncture, as well as those specifically for the indication of abnormal bleeding like TXA.

To pare down the scope of the material, we took a four step approach to structuring this KQ about harms.

- Summarizing harms detected within clinical trials included in this review. This has limitations since many of the studies are small, with a range in size of 14 to 894 and a median total study population of 80. Thus they are not well-suited to detecting events that are rare but may be serious or affect a specific subgroup of women.
- Compiling the key content of FDA documents and package inserts for specific products addressed in this review. This however lacks specificity as many of these products have multiple indications and the concerns may not be as applicable to the population of women with AUB or to the dose and duration of use for treating AUB. Furthermore symptoms and harms are reported in these documents that may not be statistically, meaningfully different between the active agent and the placebo.
- Searching for surveillance studies that aimed to examine risk of harm in large populations of individuals (i.e., 1600 or more) using the specific intervention. This last step was done using a separate search described in greater detail in methods. We restricted summarizing results from harms surveillance studies to: metformin, exenatide, progestogens, cabergoline, LNG-IUS, contraceptive vaginal ring, and TXA.
- Providing information about existing contemporary reviews and guidance on harms for common medications with broad indications. Like the second approach it is important to note that these extant literature reviews reflects varied indications and populations that may not be directly applicable to use for AUB.

The organization of this chapter includes evidence about harms from these sources in the following order:

- Harms identified in randomized trials included in this review.
- Harms flagged in FDA package inserts and regulatory proceedings.
- Harms investigated in large surveillance studies of metformin, exenatide, relevant progestogens, cabergoline, LNG-IUS, contraceptive vaginal ring, and TXA.
- Contemporary reviews that include review of harms.

We present this summary of harms in the same order of KQs and intervention methods as the results for our KQs. Interventions for irregular uterine bleeding are present before those for abnormal cyclic uterine bleeding.

Key Points for Harms of Reviewed Treatments

- Metformin is associated with increased risk of gastrointestinal symptoms like diarrhea and abdominal pain. Symptoms can be reduced by slowly increasing the dose. Severe harms including lactic acidosis, serious hypoglycemia, and liver failure, studied among populations of adult diabetics, occur at incidence rates below 1 in 10,000 and may be as low as 1 in 100,000 person-years of exposure.
- Progestogens are associated with a number of common side effects of hormonal preparations including weight gain, fluid retention, abdominal pain, nausea, change in mood, and change in appetite. Abnormal uterine bleeding is itself a common side effect of progestogen only interventions.
- COCs have commonly recognized side effects that include edema, breast tenderness, nausea, headache, and skin changes. Known contraindications, including advancing age, smoking, and high risk of thrombosis, apply when considering use of COCs for irregular

bleeding. Selected COC formulations may have lower risk of deep vein thrombosis than others.

- Cabergoline has few known distinct harms; however, data is inadequate to assess risk in young women without elevated prolactin.
- LNG-IUS has few serious harms after insertion. Irregular bleeding, especially early after insertion is the most commonly reported side effect. Painful insertion occurs in roughly 1 of 100 procedures; 3.2 of 100 insertions are technically difficult, and uterine perforation occurs in 0.9 to 2.6 cases per 1,000. The LNG-IUS is not associated with increased deep vein thrombosis risk.
- NSAIDs have common harms that include abdominal pain, nausea, gastritis, and lightheadedness/dizziness. Gastrointestinal bleeding is a serious side effect related to total dose and duration of use; however, even short-term use can increase risk. The risk of gastrointestinal bleeding from low-dose, intermittent NSAID use is poorly characterized.
- TXA use is associated with headache, nasal and sinus symptoms, back pain, and abdominal pain in more than 10 percent of those taking the drug. Joint pain, muscle cramps, migraine, anemia and fatigue occur in more than 5 percent. Rare events are less well characterized and may include thrombosis, anaphylaxis, and visual disturbances. TXA is contraindicated in those with higher risk of thrombosis.
- Contraceptive vaginal ring has similar side effects to COCs including breast tenderness, nausea and headache. Ring users also experience local problems including leucorrhea, vaginitis, and ring-related events including expulsion, foreign body sensation, and coital problems. The contraceptive vaginal ring is not recommended for use in cigarette smokers over age 35.
- Other than COCs, progestogens, and the LNG-IUS, the available data may not apply well to populations of young women using these treatments.

Detailed Synthesis

Harms Related to Metformin

Information about Metformin from Included Trials

Metformin was investigated in two placebo controlled trials[51,52] and in two arms of a three-arm trial in which two arms included metformin:[53] one metformin alone and another with combined oral metformin and exenatide weekly injections. Doses used in these studies, after an initial 1 week dose ramp up were 850 mg twice a day,[51] 500 mg 3 times daily,[52] and 1,000 mg twice daily.[53] Combined, the three RCTs, with four total metformin arms, administered the drug to only 77 women, 20 of whom were also receiving another agent.[51-53] This provides insufficient power to detect events that occur at the level of 1 to 5 percent or lower that are typically of concern for harms. It also provides insufficient power to conclude that specific symptoms were statistically more common among those treated than among the 33 women who received placebo in two studies.[51,52] Women receiving metformin did report gastrointestinal symptoms, including diarrhea, abdominal pain, and nausea at higher absolute numbers than those in the placebo or exenatide only groups,[52,53] and the study reporting withdrawals[51] documented 3 times as many women on the active drug withdrew from the trial for side effects (15/45 vs. 5/47; $p<0.05$).

Information About Metformin From FDA Documents and Package Inserts

Increased gastrointestinal complaints are consistent with the documented side effects listed in the package insert for metformin which include: diarrhea, nausea/vomiting, flatulence, indigestion, and abdominal discomfort as events that are the most common and expected to occur in more than 5 percent of those who initiate the drug.[96] Of note, it is recommended that the dose be increased gradually over 1 week or more precisely because these effects are common and can be reduced by gradual introduction of the drug. The most serious known side effect of metformin is lactic acidosis which occurs when lactate accumulates in the blood and decreases blood pH. The package insert includes a boxed warning for this concerning effect.[96] Little is known about how common lactic acidosis might be among reproductive-age women, with PCOS and not type 2 diabetes, similar to those in the study or for whom the intervention might be considered as part of primary care management of irregular uterine bleeding.

Information About Metformin From Large Datasets

Our literature search aimed at identifying publications designed to investigate harms, required more than 1,600 exposed individuals, or for case-control analyses, case identification consistent with a base population of more than 1,600. We identified four publications focused on metformin harms.[97-100]

The Toxic Exposure Surveillance System database of the American Association for Poison Control Centers provided data from 1996 through 2000 for accidental and intentional over ingestion and unintentional misuse of metformin for 4,072 cases.[97] Fifty-nine percent were women and the majority was adults. Children under 12 had few serious side effects and no deaths. Among adults, harms were evenly distributed across ages with a trend for more serious outcomes in the elderly. In all groups lactic acidosis was rare (1.6%) and hypoglycemia at 2.8 percent was more common that previously reported. Given all individuals had unintended or higher than therapeutic doses, they also observed elevated creatinine levels, an increased anion gap, hypotension, and coma among those hospitalized.

The first publication focused on harms of intended use was published in 2003 to assess incidence of serious acute liver injuries in patients on hypoglycemic agents.[98] The population comprised the 171,264 members of five health maintenance organizations receiving oral diabetes medications. They identified 35 cases of acute liver failure, not known to be attributable to another cause. Incidence per 1,000 person-years of use was not statistically meaningfully different by medication used, after adjusting for other comorbidities and confounders. Overall occurrence was roughly 1 case per 10,000 person-years in this population of all adult diabetics.[98]

In 2008, an analysis using the U.K. General Practice Research Database undertook an analysis of the risk of lactic acidosis and hypoglycemia among 50,048 type 2 diabetics using oral medications.[99] The average age of patients included in the analysis was 60.7 ± 11.7 and 54.8 percent were women. They determined the incidence rate of lactic acidosis was 3.3 per 100,000 person-years among metformin users and 4.8 per 100,000 person-years among those on sulfonyl ureas. The adjusted odds ratios for both lactic acidosis and severe hypoglycemic episodes were significantly higher for those on sulfonyl ureas than metformin with a more than 2-fold elevation in risk. However this analysis also did not include individuals taking metformin for indications other than diabetes.

A retrospective cohort of more than 44,169 diabetic patients in a prepaid health plan followed for an average of 4.2 years evaluated use of endoscopy.[100] The exposure of interest was defined by prescription of specific diabetes medications and the outcome of interest was lower

gastrointestinal tract endoscopy including flexible sigmoidoscopy and colonoscopy. The analysis was undertaken in part out of concern that therapy with metformin, with attendant risk of gastrointestinal side effects, could increase use of lower tract endoscopy. Forty-seven percent of participants were women with an average age of 66. The authors found that rates of endoscopy were higher among all groups of diabetics on medications, including those using insulin. Taking into account the precision of the estimates, there was no evidence that metformin led to excess use compared with other medications either in the window immediately after initiation or with chronic use. Overall, the higher use of endoscopy may simply reflect greater screening and prevention vigilance among these patients with a chronic disease. No comparison is offered to rates among diabetics controlled with diet and exercise alone.

Information About Metformin From Systematic Reviews

Estimates for withdrawals related to inability to tolerate the drug in included trials are consistent with the meta-estimate in a recent systematic evidence review on management of obesity. The AHRQ Screening and Management of Obesity in Adults[101] evidence review reported a risk ratio of 3.92 (95% CI, 1.23 to 12.57) for withdrawals in metformin-treated groups compared with placebo in trials aimed at weight loss and not diabetes management.[101] The report likewise found excess complaints of gastrointestinal symptoms but was not able to quantify risk and noted that evidence about harms is insufficient to inform care.[101]

Similar to the surveillance data, a Cochrane pooled analysis of comparative data from 347 trials found an upper limit of 4.3 cases of lactic acidosis per 100,000 patient-years among metformin-treated diabetic patients.[102] The analysis indicated no significant difference in mean treatment levels or net change from baseline for lactate for metformin users as compared with users of other therapies represented in the included trials.[103] This review also notes that the only evidence for lactic acidosis associated with metformin use is based on approximately 330 cases reported in the literature.[102] The 2011 AHRQ comparative effectiveness review (CER) Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update[104] included 140 trials with a meta-analysis. Across all data sources in their review, the reviewers concluded there was high grade evidence that metformin alone and in combination with other diabetes medications was associated with greater occurrence of gastrointestinal side effects than with other agents alone or in combinations that did not include metformin. Nonetheless the overall safety profile and effectiveness of metformin led to the conclusion that metformin was the first-line agent for initial management of type 2 diabetes. The authors take care to point out that even among trials for a chronic condition like type 2 diabetes, longer term surveillance for harms does not exceed 2 years. As in diabetes, women with abnormal bleeding might wish to consider chronic treatment and the literature to assess safety of continued use for any indication is scant.

Within a number of reviews of oral diabetes agents[105,106] metformin is typically found to have a favorable safety profile when compared with other medications and is often noted to be first-line therapy in part for this reason. Relative safety in the context of other options for treating diabetes is not directly applicable to use for improving menstrual cycle regularity, however there are no physiologic reasons to expect that younger individuals without diabetes would experience greater risk.

Harms Related to Exenatide

Information About Exenatide From the Included Trial

A single RCT in this review investigated exenatide, finding that alone it was less effective than metformin, but that when combined the results were superior to either agent alone for improving cycle regularity in women with PCOS.[53] Exenatide is injected weekly and is generally administered as a second agent among those with diabetes that is insufficiently controlled on a single agent. The trial included in this review allocated women with PCOS to three groups: 1,000 mg of metformin twice daily, exenatide 10 mcg per day, or both.[53] Nausea, diarrhea, and bloating were more common in the arms taking metformin. No harm was more common in the exenatide group except injection site pain or bruising which was de facto restricted to groups using exenatide. Comparisons across groups of 20 are underpowered to detect differential harms across groups or to detect more rare and potentially serious harms.

Information About Exenatide From FDA Documents and Package Insert

The package insert for exenatide notes that hypoglycemia is a common adverse effect but does not specify what proportion of those prescribed the drug might experience low blood sugar.[107] Events that occurred in 2 percent or more of new users of exenatide when added to a regimen with metformin or a sulfonyl urea include: nausea, vomiting, diarrhea, feeling jittery, dizziness, headache, dyspepsia, asthenia which is a lack of strength or energy, gastroesophageal reflux, and increased sweating. Postmarketing experience includes reports of: injection-site reactions; generalized pruritus and/or urticaria; macular or papular rash; angioedema; anaphylactic reaction; increased international normalized ratio with concomitant warfarin use sometimes associated with bleeding; nausea, vomiting, and/or diarrhea resulting in dehydration; abdominal distension; abdominal pain; eructation; constipation; flatulence; acute pancreatitis; hemorrhagic and necrotizing pancreatitis sometimes resulting in death; dysgeusia; somnolence; altered renal function, including increased serum creatinine; renal impairment; worsened chronic renal failure or acute renal failure (sometimes requiring hemodialysis); kidney transplant and kidney transplant dysfunction; and alopecia (Byetta Package Insert, 2011).[107]

Information About Exenatide From Large Datasets

Surveillance studies have all focused on acute pancreatitis which is suspected of being a rare but important side effect. Two analyses in large patient pools did not identify an association,[108,109] while a third publication with data from the FDA post marketing surveillance database did see increased risk for both exenatide and another drug with similar but not identical mechanism, sitagliptin.[110]

The two claims-based analyses relied on large databases of health plan enrollees: The Ingenix Research Datamart[108] and the Normative Health Information database.[109] The first examined 27,966 individuals who began exenatide and 16,276 who started sitagliptin.[108] During 1 year of followup, acute pancreatitis occurred in 0.13 percent of those on exenatide and 0.12 percent of those on sitagliptin. In adjusted models, relative to comparison cohorts within the health plan the relative risk of acute pancreatitis was 1.0 for both groups with confidence bounds from 0.6 to 1.7 and 0.5 to 2.0 respectively. The second analysis included 25,719 new users of exenatide compare to 234,536 new users of other diabetes medications.[109] The groups differed in important ways including more obesity and concomitant diabetes medications among those using exenatide. In adjusted models to control for these and other factors, there was no increase in use

for current or recent use but an elevation in risk for past use. This was compared with a matched case-control analysis that found no association for any category of current, recent, or past use. This is compatible with those with past use having unknown additional comorbidity or discontinuing use because of other serious health events. The authors conclude overall there was not increased risk of pancreatitis among those taking exenatide.

The FDA surveillance data compared adverse events for exenatide to those for other drugs in the database.[110] They found the odds of being on exenatide were more than 10-fold higher than the control drug for pancreatitis. Pancreatic cancer was almost 3-fold higher. The sole control for confounding was the use of those on other drugs in the registry as a comparator. The authors note that the FDA data is limited by incomplete data and reporting bias; notably they lack information about obesity and individual behaviors such as alcohol use and the risk models are not adjusted for these confounders.

Information About Exenatide From Systematic Reviews

Systematic reviews of diabetes medications (including the AHRQ report above on obesity treatment[101]), a detailed CER conducted by the United Kingdom's National Health Service, and a Cochrane analysis including exenatide, reveal gastrointestinal issues, particularly nausea and vomiting, and hypoglycemia as the most commonly observed side effects observed in those initiating therapy with this agent.[101,111,112]

Harms Related to Progestogens

Information About Progestogens From Included Trials

A single RCT included in this review investigated progestogen use for improving cycle regularity.[49] The two agents used in this comparative effectiveness trial were 20 mg of oral dydrogesterone, each day for 10 days, or 90 mg of micronized progesterone gel vaginally every other day for 10 days. The authors' intent was to demonstrate that both oral and vaginal administration improved cycle control which was the case compared with baseline. However power calculations did not indicate the equivalence band desired and the overall study was small (n=69). They report the only adverse events experienced were in the micronized vaginal progesterone gel group and included one episode each of groin pain, ovarian cyst, and 5-kg weight gain. These events were too rare given the small study size to meaningfully assert comparability or excess of harms between groups. Six patients in each treatment group withdrew from the study (reasons not given), suggesting there was not a large discrepancy in willingness to stay on study drug.

Eight studies of treatments for abnormal cyclic bleeding (KQ1B) included a progestogen as a comparator. MPA was a comparator in three studies,[60,62,79] one of which included DMPA as a third comparison arm.[62] Five studies compared LNG-IUS, TXA, an NSAID, or the contraceptive vaginal ring to norethisterone[64,70,74,80,84] and one of these studies also included a third arm using the progesterone-impregnated intrauterine coil as a comparator.[74] Harms reported with this class of drug include: breakthrough bleeding; spotting; change in menstrual flow; amenorrhea; headache; nervousness; dizziness; edema; increases or decreases in weight; change in cervical secretions; cholestatic jaundice, breast tenderness and galactorrhea; skin sensitivity reactions consisting of urticaria, pruritus, edema and generalized rash; acne, alopecia and hirsutism; rash (allergic) with and without pruritus; anaphylactoid reactions and anaphylaxis; depression; pyrexia; fatigue; insomnia; nausea; and somnolence.[113-116] Most studies reviewed were small and

did not systematically compare adverse events across interventions groups. In all but one case, progestogens were a comparator that was hypothesized and found to perform less well than the intervention under study. The one exception was a direct comparison of two routes of delivery discussed above.[49] We consider COCs and the LNG-IUS in their own section.

Information About Progestogens From FDA Documents and Package Inserts

We have summarized information for progestogen only methods included in this review. The label for Crinone, the progesterone vaginal gel, reports adverse events seen in the three clinical studies for secondary amenorrhea in women taking either 4-percent or 8-percent strength Crinone along with estrogen and occurring in 5 percent or more of women.[114] These are given as: abdominal pain (5% in patients taking 4% strength, 9% in patients taking 8% strength, respectively); appetite increased (5%, 8%); bloating (13%, 12%); cramps not otherwise specified (19%, 26%); fatigue (21%, 22%); headache (19%, 15%); nausea (8%, 6%); back pain (8%, 3%); myalgia (8%, 0%); depression (19%, 15%); emotional lability (23%, 22%); sleep disorder (18%, 18%); vaginal discharge (11%, 3%); upper respiratory tract infection (5%, 8%); and pruritus in genital area (2%, 6%).[114] The package insert for vaginal progesterone gel includes a warning that "physicians should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis)."[114]

This profile of complaints is similar among smaller groups of women who receive the drug as part of treatment for infertility care. One of the specific agents studied among women with irregular menses, dydrogesterone, is not available in the United States. This compound has been associated with risk of onset of acute porphyria. Porphyria is a genetic condition in which individuals have a range of severities of defects in the enzyme pathways that produce heme. The insert advises prescribing only for compelling reasons. Our review team does not find evidence that other progestogens are associated with acute onset of porphyria symptoms.

The DMPA label[115] includes a warning to women who may become pregnant while using the drug or find themselves exposed to the drug during the first 4 months of pregnancy regarding the risk of hypospadias; the risk of hypospadias, usually 5 to 8 per 1,000 male births in the general population, may be approximately doubled with exposure to these drugs.[115] Additionally, there have been undesirable effects at the site of injection, such as residual lump, change in skin color, or sterile abscess.[115]

Information about Progestogens from Large Datasets

The specific compounds used for irregular uterine bleeding or abnormal cycle bleeding were not addressed in large surveillance studies or in systematic review that compiled information about harms separate from their inclusion in COCs with the exception of DMPA and norethindrone in progestin-only pills.

As noted, we did not attempt to review the surveillance literature related to harms of oral contraceptives or specific progestogens in COCs. We did however seek large scale primary studies related to harms of progestogen-only formulations such as DMPA. Four studies, one conducted in Europe, one in Turkey, and two in Africa, described harms associated with DMPA.[117-120] A single cross-cutting study of contraceptive risks included norethindrone-alone pills.[121]

A Danish case-control study that included 64,548 women with fractures indicated an association with DMPA use (OR=1.44; 95% CI, 1.01 to 2.06); this however was not adequately controlled for factors that may confound the relationship, such as the potentially increased use of

DMPA among smokers or those with lower body mass index which are both also associated with fracture risk.[118] A study in South Africa evaluated bone density in 3,487 black, reproductive-age women using injectable progestogens as contraception and reported decreased bone density by measurement of heel bone density; this effect was reversible within 2 to 3 years of discontinuing the injected progestogen across age categories of users.[119] These findings are compatible with data from smaller studies which they review well in their publication.

DMPA has been associated in observational studies with deep venous thrombosis.[117] However, other work comparing those who use medications for menorrhagia has documented increased risk among women who use TXA, mefenamic acid, and norethisterone, suggesting that the increased risk of thrombosis may be an example of confounding by indication. Such confounding suggests that the reason for which the medication is administered itself increases risk of the adverse outcomes.[122] In a comprehensive study of 9,262 DMPA users in Turkey conducted between 1996 and 2004, deep vein thrombosis was not observed.[120] The most common adverse effects reported were menstrual disturbances (80%), weight gain (10%), bloating, breast pain, headache, mood change, and sexual difficulties (each reported by more than 1%). More than one-third of women discontinued the method with the most common reasons for discontinuing other than desiring to conceive being irregular menses and side effects.

A 2012 publication about hormonal contraceptive methods and risk of thrombotic stroke and myocardial infarction, estimated risk based on person-years of exposure to specific contraceptive methods in a cohort of 15 years duration.[121] In a total of 85,874 women-years of observation, norethindrone progestin-only pills were not statistically significantly associated with increased risk of either stroke or myocardial infarction.

Information About Progestogens From Systematic Reviews

A Cochrane review examining the use of progestogens for the treatment of heavy menstrual bleeding found that progestogens had a generally better side effect profile than danazol, with lower incidence of side effects such as headache, weight gain, and skin changes; however, breast changes were relatively more common in the progestogens group.[123] In the context of evaluating progestogen-only pills for contraception, another Cochrane review found inter-cycle bleeding and cycle irregularity to be some of the most common reasons for treatment discontinuation represented in included trials.[124]

Harms Related to COCs

Information About COCs From Included Trials

Our review included six RCTs examining COC use in women with abnormal uterine bleeding.[50, 59, 61, 68, 82, 83] Due to the low power of these three medium sized RCTs and three small RCTs for detecting adverse events, reports of potential harms in these publications are largely limited to descriptive text rather than quantitative comparisons.

Among women with irregular menses only (KQ1A), one study treated patients with COCs. Davis and colleagues[50] assessed a triphasic pill in which the estrogen was ethinyl estradiol and the progestogen was norgestimate. Their trial randomly assigned 201 women to the oral contraceptive arm or a placebo. Authors do not provide detailed description of adverse events, noting that the incidence was low and comparable between the two groups. Four women in the COC group and three in the placebo group discontinued use after adverse events. Sixteen percent

of those on active drug and 19 percent of those receiving placebo withdrew prior to completion of the trial.

Two trials assessing the use of estradiol valerate and dienogest in women with abnormal cyclic uterine bleeding (KQ1B) each found that 9 to 10 percent of women discontinued therapy with the COC regimen due to side effects.[82,83] The type and incidence of adverse effects noted in these two studies of estradiol valerate and dienogest are similar to those noted in the package insert for this combination.[125]

The trial examining therapy with ethinyl estradiol and norethindrone acetate reported that five women discontinued the study due to adverse events (approximately 25%), noting that the most comment events included intermenstrual bleeding, menstrual disorder, and headache.[61] The two studies involving use of ethinyl estradiol and levonorgestrel did not describe potential harms associated with treatment failure, other than noting the incidence of treatment failure.[59,68]

Information About COCs From FDA Documents and Package Inserts

The package inserts are similar for all combined estrogen and progestogen oral contraceptive pills. The warning for combined pills notes:

> Cigarette smoking increases risk of serious cardiovascular events from combined oral contraceptive (COC) use. This risk increases with age particularly in women over 35 years of age and with the number of cigarettes smoked. For this reason, COC's should not be used by women who are over 35 years of age and smoke.[126-128]

Other serious harms associated with COCs include thrombophlebitis and venous thrombosis with and without embolism, arterial thromboembolism, pulmonary embolism, myocardial infarction, cerebral hemorrhage, cerebral thrombosis, hypertension, gallbladder disease and benign liver tumors. A complete listing of package insert adverse events for this and other oral contraceptives reviewed in this report is included in Appendix N. Package inserts do not generally include information about the expected population incidence of these harms.

The majority of primary care providers and many women are aware of the most serious risks of COCs and of more common side effects such as edema, nausea, vomiting, skin changes, and gastrointestinal symptoms. Among more common side effects are also changes in cycle characteristics themselves including spotting/breakthrough bleeding, lack of menses, and change in characteristics of menstrual flow.

Adverse events for specific COCs studied for heavy menstrual bleeding in this review include Nordette-28® (0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel). The package insert reports based on data from case control studies, the relative risk for superficial venous thrombosis is three times higher in users of the COC compared with nonusers; the risk of deep vein thrombosis or pulmonary embolism is 4 to 11 times higher, and 1.5 to 6 times higher in women predisposed to venous thromboembolic disease.[127] The incidence of deep vein thrombosis and pulmonary embolism for users of low-dose (i.e., less than 0.05 mg ethinyl estradiol) COCs is up to 4 per 10,000 woman-years compared with 0.5 to 3 per 10,000 woman-years for nonusers, although this risk is less than the risk associated with pregnancy (6 per 10,000 woman-years).[127] A large postmarketing study noted that the Nordette label information reports a relative risk of thrombotic strokes ranging from 3 for normotensive users to 14 in women with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for

nonsmokers using oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users, and 25.7 for users with severe hypertension.[127]

Label information on estradiol valerate and dienogest (Natazia®) reports two cases of myocardial infarction and two cases of rupture ovarian cyst from clinical trials, along with known serious risk of other cardiovascular events, vascular events, and liver disease (the estimated attributable risk of liver adenomas is 3.3 cases per 100,000 COC users).[125] In clinical studies of the drug, 11.4 percent of women discontinued treatment due to an adverse reaction, most commonly: menstrual disorder (metrorrhagia, menorrhagia, menstruation irregular, genital hemorrhage, vaginal hemorrhage, dysfunctional uterine bleeding; 2.3%); mood changes (depression, mood swings, mood altered, depressed mood, dysthymic disorder, crying; 1.2%); acne (1.1%), headache (including migraines; 1.1%), and weight increased (0.7%).[125]

Postmarketing reports with Natazia include: venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, cerebral thrombosis, myocardial infarction and stroke); hypertension; gallbladder disease; hepatitis; hypersensitivity; fluid retention; hypertriglyceridemia; dizziness; chloasma; angioedema; erythema nodosum; erythema multiforme; vulvovaginal candidiasis; and gastrointestinal symptoms.[125]

Information About COCs From Large Datasets

More than a hundred publications about harms (and preventive effects) of COCs are available and full review was beyond the scope of this review. The systematic reviews featured below include contemporary pills formulations and their harms.

Information About COCs From Systematic Reviews

Two recent systematic reviews have identified significant increased risk of deep venous thrombosis among users of oral contraceptives, though the size of risk varied significantly among different COC regimens and appeared lowest for agents containing levonorgestrel or norgestimate.[129,130] One Cochrane review has evaluated the potential association between COC use and weight gain, finding insufficient evidence to make conclusions and noting the likelihood that there is no large association between COCs and increased weight during therapy.[131] Other Cochrane reviews have assessed the relative efficacy and safety of various oral contraceptive regimens; these reviews note variability in the type and incidence of adverse events among included studies and comment that adverse event reporting among these studies was generally of lower quality than expected, recommending better tracking of side effects in future studies as well as systematic capture of patient reasons for treatment discontinuation.[132-135] One of these reviews found that the incidence of discontinuation due to side effects was lower in triphasic-treated patients as compared with their monophasic-treated counterparts.[134] The one Cochrane review assessing the use of COCs in the setting of heavy menstrual bleeding identified only one small crossover trial, which did not include description of adverse events.[36]

Harms Related to Cabergoline

Information About Cabergoline From Included Trials

A single exploratory study, with 29 participants among whom 14 had PCOS and 15 were normal controls, randomly assigned 16 women to cabergoline and 13 to placebo for 4 months.[55] The authors did not report adverse events and all women completed the trial.

Information About Cabergoline From Package Insert

The package insert for this drug intended to treat elevated prolactin levels provides data about the risk of side effects in comparison to placebo in a 4-week study and compared with bromocriptine which is another medication for prolactinoma treatment.[136] In Table 21 we summarize the incidence of cabergoline side effects that occurred in more than 5 percent of those on the drug, as well as 4 week experience of side effects among individuals on placebo. We did not identify large dataset analyses aimed at surveillance for harms.

Table 21. Side effects reported in cabergoline trials

Side Effect (% participants experiencing)	Placebo at 4 Weeks	Cabergoline at 4 Weeks	Cabergoline at 8 weeks
Nausea	20	27	29
Headache	25	26	26
Dizziness	5	15	17
Asthenia	10	9	6
Constipation	0	10	7
Abdominal pain	5	5	5
Somnolence	5	5	2
Fatigue	0	7	5
Depression	5	3	3
Hot flashes	5	1	3
Dyspepsia	0	2	5

Information About Cabergoline From Large Datasets

One harms surveillance study using the U.S. Adverse Event Reporting System Database [137]and two analyses done with data from the UK General Practice Research Database [138,139] have linked drugs typically used to treat Parkinson's disease, including cabergoline, to risk of harms. Comparing cabergoline, an ergot derived drug, to nonergot derived drugs, or no medication, these descriptive studies report new cardiac valve regurgitation occurred almost 5 times more often among those receiving cabergoline in the UK case control study[137] and more than 100-fold more often in the United States adverse events registry.[137] The latter publication followed the former which may have raised awareness and amplified reporting. The research team using United States data also reported increased odds of other forms of noncardiac fibrotic reaction in the pleura, retroperitoneal spaces, and lungs. Most recently, cabergoline in the UK database was link with doubling of heart failure risk.[139] Notably these populations are substantially older and highly likely to have a specific comorbidity (Parkinson's) which may also modify risk and which makes estimation of risk in other groups infeasible. No direct surveillance data is available to inform estimation of risk in reproductive-age women.

Information About Cabergoline From Systematic Reviews

Several systematic reviews have explored the safety and efficacy of cabergoline for treatment of a range of conditions. Two Cochrane reviews on ovarian hyperstimulation syndrome and restless leg syndrome, respectively, each assessed a small pool of available trials, finding no significant difference in overall incidence of adverse events between cabergoline and comparators.[140,141] A meta-analysis of dopamine receptor agonist use among individuals with Parkinson's disease found a relative risk of 6.38 (95% CI, 3.17 to 12.81) for moderate to severe valvular regurgitation[142]; a similar analysis of cabergoline use in hyperprolactinemia also found a significant increase in risk of valve regurgitation, though this echocardiographic finding in this

patient population was clinically asymptomatic in all patients and participants were certain to be older and more frail than women who would use the treatment for irregular uterine bleeding.[143]

Harms Related to Lifestyle and Behavioral Interventions

Information Across Sources for Diet and Exercise

The single RCT of diet and exercise intervention was conducted in teens with irregular menses and did not identify adverse effects.[56] One acupuncture trial included 34 women randomized to a walking regimen who reported no adverse events or injuries.[57] However it is important not to assume that lifestyle and behavioral interventions such as diet and exercise are without risks. The U.S. Preventive Services Task Force report on Screening and Management of Obesity in Adults[101] provides a clear and succinct description of the potential harms stating:

> Possible harms that could accrue from [these] interventions include bone loss and increased fracture risk, injuries from increased physical activity, decreased self-esteem from being labeled as obese or failure to lose weight, use of extreme or unhealthy dietary approaches, and weight cycling.[101]

Harms Related to Acupuncture

Information Across Sources for Acupuncture

One study of acupuncture, that compared two strategies for selecting placemen of needles, did not discuss harms or withdrawals.[58] The other RCT reports only local redness or hematomas occurring in 10 percent of those receiving acupuncture in 14 sessions over 16 weeks.[57] Two of 33 women in the acupuncture group reported other side effects which were dizziness and nausea, while the exercise and no intervention control group did not report any events.

A number of Cochrane reviews have explored the use of acupuncture for treatment of a variety of women's health issues, ranging from dysmenorrhea to endometriosis-related pain to induction of labor; across the board, these reviews found that potential harms of acupuncture have not been well studied and are often omitted from trial reports completely, noting that investigation of possible adverse effects is an important consideration for future research involving this therapeutic approach.[144-147]

Harms Related to LNG-IUS

Information About LNG-IUS From Included Trials

One trial did not provide any information about harms or adverse effects.[59] Two trials stated that there were no serious adverse effects related to either treatment.[64,65] In one trial with 39 participants, one participant discontinued LNG-IUS therapy (5%) and five participants discontinued cyclic COC (26%).[61] One trial reported side effects in a table without comparative statistics.[63]

One trial (n=165) reported that no deaths or drug-related serious adverse events occurred during the study.[60] Six participants in the LNG-IUS group (7%) and two in the oral MPA group (2%) discontinued treatment because of adverse events.[60] The LNG-IUS was expelled in four participants (5%); two other participants had the LNG-IUS removed due to adverse effects.[60] No uterine perforations or pregnancies were observed during the study.[60] Other treatment-emergent

adverse events reported during the study and occurring in at least 5 percent of women in any treatment group were reported in a table without comparative statistics.

One trial reported 242 adverse events among 51 participants, with 158 in the LNG-IUS group and 84 in the mefenamic acid group.[63] The LNG-IUS was expelled in two participants (8%); one of these had chlamydial endometritis.[63]

Information About LNG-IUS From FDA Documents and Package Insert

In October 2009, the prescription label for the LNG-IUS available in the United States was updated though a process with the FDA.[148] This revision was made for the new indication: treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception.[149]

According to the package insert, the most common (i.e., more than 10 percent) adverse reactions reported in clinical trials of LNG-IUS are: uterine/vaginal bleeding alterations (51.9%), amenorrhea (23.9%), intermenstrual bleeding and spotting (23.4%), abdominal /pelvic pain (12.8%), and ovarian cysts (12%).[148] The data provided reflect the experience with the use of Mirena brand LNG-IUS in the adequate and well-controlled studies for contraception (n=2,339) and heavy menstrual bleeding (n=80). For the treatment of heavy menstrual bleeding indication (n=80), the subjects included women aged 26 to 50 with confirmed heavy bleeding and exposed for a median of 183 treatment days of Mirena (range, 7 to 295 days).

The adverse reactions seen across the two indications overlapped, and are reported using the frequencies from the contraception studies. The less common (i.e., between 5% and 9% of users) adverse reactions are: headache/migraine (7.7%), acne (7.2%), depressed/altered mood (6.4%), menorrhagia (6.3%), breast tenderness/pain (4.9%), vaginal discharge (4.9%), and IUD expulsion (4.9%). Other relevant adverse reactions occurring in fewer than 5 percent of subjects include nausea, nervousness, vulvovaginitis, dysmenorrhea, back pain, weight increase, decreased libido, cervicitis/Papanicolaou smear normal/class II, hypertension, dyspareunia, anemia, alopecia, skin disorders including eczema, pruritus, rash and urticaria, abdominal distention, hirsutism, and edema.[148,150]

Information About the LNG-IUS From Large Datasets

Large scale surveillance for harms provides important information to patients to assure informed decisions about risks. This data includes information about complications with insertion. In the New Zealand monitoring system which includes 3,519 insertions, difficult insertions occurred in 3.6 percent of procedures and were not well predicted by nulliparous status of noncontraceptive use of the IUD. Pain on insertion occurred for 1 percent of patients and 0.5 percent of attempts to insert could not be completed.[151,152] Uterine perforation rates in three large datasets ranged from 0.9 to 2.6 cases per 1,000.[151,153,154] Authors of each of these studies, as well as those of another report from four national pharmacovigilance centers in Europe confirm, that perforations may not consistently be associated with painful insertions and that only a small portion (less than 10%) are recognized at the time of the insertion.[155]

In surveillance data, the LNG-IUS in not associated with increased risk of deep vein thrombosis,[117] including in more than 8 million women-years of observation among Danish women.[156] The anecdotally reported complaint of hair loss is supported by a single study in New Zealand by surveying women in the national registry. They found five cases of alopecia (two recovered, one not, and two still unknown) and estimated incidence to be 1.8 per 1,000 users.[153]

A 2012 publication about hormonal contraceptive methods and risk of thrombotic stroke and myocardial infarction, estimated risk based on person-years of exposure to specific contraceptive methods in a cohort of 15 years duration.[121] In a total of 184,875 women-years of observation, the LNG-IUS was not statistically significantly associated with increased risk of myocardial infarction, and appeared, relative to women not using hormonal methods, to offer protection from stroke (RR=0.73; 95% CI, 0.54 to 0.98).

Information About the LNG-IUS From Systematic Reviews

Systematic reviews report adverse events similar to those noted in the package insert,[148] with weight gain, bloating, acne, nausea and breast pain as the most commonly observed side effects. These systematic reviews also comment on the risk of spontaneous device expulsion, reporting an incidence of 5 to 16 percent.[157-159]

Harms Related to Contraceptive Vaginal Ring

Information About Contraceptive Vaginal Ring From Included Trials

The vaginal ring was used in a single study in this review as a treatment for heavy menstrual bleeding and was found to be similar in effectiveness to oral norethisterone.[84] The contraceptive vaginal ring provides a steady release of 15 mcg of ethinyl estradiol and 120 mcg of etonogestrel daily and is used vaginally for 3 weeks per cycle and then removed for 1 week. Following three cycles of treatment, this study reported that the incidence of nausea, headache, and breast tenderness was comparable in both treatment groups. The contraceptive vaginal ring users were less likely to report breakthrough bleeding than the women taking norethisterone. No ring expulsions were reported. Local events, including vaginal discomfort, vaginitis, foreign body sensation and coital problems were reported more frequently in ring-users, but no one discontinued treatment due to adverse events.

Information About Contraceptive Vaginal Ring From FDA Documents and Package Insert

The package insert lists the most common harms reported by 5 to 14 percent of women in clinical trials including vaginitis, headache, upper respiratory infection, vaginal secretion, sinusitis, nausea, and weight gain.[160] The adverse events leading to discontinuation of treatment in 1 to 2.5 percent of women include device-related events (e.g., foreign body sensation, coital problems, and expulsion), vaginal symptoms, headache, emotional lability, and weight gain. The package insert also warns against use of the vaginal contraceptive ring in cigarette-smokers over age 35.

Information About Contraceptive Vaginal Ring From Large Data Sets

We identified three studies reporting data on harms from large studies of contraceptive vaginal ring users.[121,161,162] A 15-year Danish cohort study that included over 38,000 person-years of vaginal ring use reported an elevated adjusted relative risk of 2.5 (95% CI, 1.4 to 4.4) for thrombotic stroke and 2.1 (95% CI, 0.7 to 6.5) for myocardial infarction compared with women (over 9 million person-years) who had not used hormonal contraception.[121] In an observational study of over 2,500 Swiss women, 20 percent (n=539) of contraceptive vaginal ring users reported 753 adverse events. The most common harms were changes in menstrual bleeding pattern (2.3%), vaginal discomfort (2.2%), leucorrhea (2.1%), mood disorders (2.0%)

and headache (1.9%).[161] This profile is similar to data from a German open label study of the acceptability of the contraceptive vaginal ring in which 431 of 5,823 (7.4%) of women discontinued use for side effects over six cycles of use. In the full cohort, 9.9% of women experienced symptoms classified as adverse events with the most common being bleeding pattern, headache (including migraine),and acne.[162] The research team reports 19 women (<0.3%) has serious adverse events each of which was an isolated event, other than dizziness which was reported by two women.

Information About Contraceptive Vaginal Ring From Systematic Reviews

A recently published review of the contraceptive vaginal ring summarized adverse events from three large trials.[163] The number of women using the contraceptive vaginal ring in these three studies ranged from 499 to 2,322. Over one half of the women (58 to 66%) reported at least one adverse event and 29 to 38 percent of these were possibly related to the contraceptive. The most frequent complaints were headache (5.8 to 7.2%), ring-related (4.4 to 6.8%), vaginitis (3.9 to 5.6%), leucorrhea (3.2 to 4.8%), and nausea (0.8 to 3.2%). Between 11 and 14 percent of women discontinued use of the contraceptive vaginal ring due to adverse events. Two women in one study had deep vein thrombosis. Hypertension was reported in four women (0.8%) in a single study. A study that investigated the effects of the device on lipid profiles reported increases in triglycerides and sex hormone binding globulin levels but total cholesterol was unchanged.

Another systematic review of COCs and bone health included one small cohort study of contraceptive vaginal ring users, noting no change in bone mineral density from baseline for the vaginal ring users compared with an increase in bone density among the control group of nonhormone users.[164] A recently published systematic review examining thrombotic risks of oral contraceptives included data from studies of the contraceptive vaginal ring.[165] The risk of venous thromboembolism for the contraceptive vaginal ring was elevated and similar to COCs containing ethinyl estradiol and gestodene (5.6-fold increase) or desogestrel (7.3-fold increase) or ethinyl estradiol and drospirenone (6.3-fold increase).[165]

Harms Related to NSAIDs

Information About NSAIDs From Included Trials

Three trials did not provide any information about harms or adverse effects.[68,73,74] Two trials reported there were no serious side effects.[75,77] Another trial reported treatment discontinuation among one person receiving mefenamic acid and one person receiving norethisterone after the third cycle.[70] A table of adverse events was presented in this study with no comparative statistics, though abdominal pain was reported in 18 percent and 20 percent of both mefenamic acid and norethisterone groups.

In one trial,[63] there were 242 adverse events noted with 158 in the LNG-IUS group and 84 in the mefenamic acid group. There were two significant adverse events in this study, one with hypertension in a patient with a history of hypertension, and one with chlamydia endometriosis resulting in LNG-IUS expulsion. Of note, a smaller proportion of patients reported abdominal pain with mefenamic acid (7.7%) compared with LNG-IUS (32.0%), though significance was not reported in the table of adverse events.

In another trial,[66] a total of 18 patients stopped treatment including three of 23 taking mefenamic acid due to poor efficacy or an unwanted event such as nausea, headache, and dizziness.

One trial[77] reported nausea and gastrointestinal disturbances in nine (16.4%) and eight (14.5%) and leg cramps in seven (12.7%) and 12 (21.8%) cases among those receiving TXA and TXA with mefenamic acid, respectively.

One small crossover trial reported no treatment discontinuations,[71] however, patients receiving TXA reported nausea, dizziness, numbness, restless legs, and headache. Vomiting and difficulty swallowing was reported by three women in the TXA group. Patients receiving flurbiprofen reported tiredness, stomach pains, and nausea.

In one trial,[67] one person discontinued mefenamic acid due to severe skin rash and itching and in another trial,[69] one person on mefenamic acid complained of gastritis. In another trial,[72] one patient had epigastric distress and four patients had nausea and vomiting on meclofenamate. However, the severity of dysmenorrhea ($p<0.006$), backache ($p<0.02$), and headache ($p<0.002$) were significantly less for patients taking meclofenamate than placebo. There was no difference in nausea or vomiting.

One trial[75] reported any side effects in 18 patients taking naproxen and in 15 patients taking mefenamic acid. Thirteen patients taking naproxen experienced gastrointestinal symptoms (i.e., nausea, diarrhea, abdominal discomfort, and anorexia) compared with six taking mefenamic acid. Central nervous system symptoms (i.e., light headedness, dizziness, tiredness, and headache) were reported by patients receiving mefenamic acid (n=6) and naproxen (n=5).

One trial[76] reported no significant differences in nausea, depression, breast symptoms, and other symptoms between mefenamic acid and placebo. However there was significant reductions in abdominal pain ($p<0.001$), headache ($p<0.001$), and diarrhea ($p<0.008$) among those taking mefenamic acid compared with placebo.

Information About NSAIDs From FDA Documents and Package Inserts

As a class, NSAIDs carry a risk of serious harms from cardiovascular thrombotic events, myocardial infarction, stroke, renal effects, and hepatic effects, along with gastrointestinal ulceration, bleeding and perforation. All drugs in this class have a boxed warning for cardiovascular and gastrointestinal risk. Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1 percent of patients treated for 3 to 6 months, and in about 2 to 4 percent of patients treated for 1 year, with trends continuing with longer duration of continuous use.[166-168] Labels note that even short-term therapy is not without risk with this drug class.

In general, NSAIDs have been commonly associated with harms including edema, abdominal pain, constipation, diarrhea, dyspepsia/heartburn, elevated liver enzymes, flatulence, gastrointestinal bleeding, nausea, vomiting, body weight changes, headache, nervousness and other manifestations of central nervous system stimulation (e.g., anxiety, insomnia, increased reflexes, tremor), symptoms associated with central nervous system inhibition (e.g., amnesia, asthenia, depression, malaise, somnolence), rash, changes in vision, dizziness/vertigo, tinnitus, and signs and symptoms suggesting urinary tract infection.

More harms information on specific drugs is limited in the package inserts, for many of the reasons given in the above discussion. In controlled studies of meclofenamate, approximately 4 percent of the patients had diarrhea severe enough to require discontinuation of the drug.[167] See Appendix M for more complete information from individual package inserts.

Information About NSAIDs From Systematic Reviews

A pooled analysis of trials in a systematic review of NSAIDs for the treatment of dysmenorrhea found that mild neurological and gastrointestinal adverse events reported at significantly greater frequency by those receiving NSAIDs as compared with those receiving placebo.[169] Another recent review underscores the risk of various gastrointestinal complaints and notes that the cardiovascular effects of the traditional NSAIDs are poorly understood and warrant further research;[103] an increased risk of nonfatal myocardial infarction was also observed in a recent systematic review and meta-analysis.[170]

Harms Related to TXA

Information About TXA From Included Trials

Within studies included in our review, similar numbers of participants withdrew from TXA and placebo or other treatment groups.[78,79] No thrombotic events were reported in the participants treated with TXA and no deaths occurred during the study. Serious adverse events reported in the TXA groups of trials included allergic reactions, headaches, and other symptoms such as tachycardia, acute bronchitis, hypoglycemia, and posttraumatic stress disorder, the latter judged to be unrelated to study treatment. There was no significant difference in the percentage of side effects reported, comparing TXA to placebo. In particular, the frequency of gastrointestinal-related adverse events was similar between groups. In another trial,[66] a total of 18 patients stopped treatment including four of 26 taking TXA due to poor efficacy or an unwanted event such as nausea, headache, and dizziness. One included trial had no withdrawals or side effects reported,[71] another reported no serious adverse effects.[80]

Information about TXA from FDA Documents and Package Insert

The companies, Xanodyne Pharmaceuticals and Ferring Pharmaceuticals, that manufacture TXA (Lysteda®) received FDA approval after submitting research findings and other data in 2009. The manufacturer conducted two placebo-controlled randomized trials; the second of which has been published.[78] The first trial randomized 304 women and compared two doses of TXA (1,950 mg and 3,900 mg daily for up to 5 days during each menstrual period) versus placebo over three cycles.[171] The data provided to the FDA for safety included these two pragmatic cluster RCTs and two uncontrolled phase three trials, and a single QT-interval phase two study. In total, these five studies described 12,169 treatment cycles, but among them only 234 women received the current recommended therapeutic dose of the medication.[172] Overall, the nature and number of adverse events did not raise any significant safety concerns. There were no venous thromboembolic events in subjects taking TXA. There were no adverse effects on vision or ocular safety concerns. There was no effect on the QT-interval. No drug-drug interactions studies were conducted. The total number of subjects in clinical trials who received TXA was considered low for evaluation of harms and drug safety.

The FDA also reviewed evidence from a database for a different formulation of TXA that included 40 cases of possible venous thromboembolism over 5 years (none in the United States), with 40 percent of these events occurring with intravenous use of the drug, and for indications other than heavy menstrual bleeding.[171] The review utilized by the FDA also documented associated instances of retinal venous and arterial occlusion and ligneous conjunctivitis.[171]

In April 2011, the prescription label and package insert for the formulation of TXA available in the United States was updated.[171] According to the current label, the most common adverse

reactions reported in clinical trials of TXA were headache (50.4%), nasal and sinus symptoms (25.4%), back pain (20.7%), abdominal pain (19.8%), musculoskeletal pain (11.2%), arthralgia (6.9%), muscle cramps and spasms (6.5%), migraine (6%), anemia (5.6%), and fatigue (5.2%); comparative statistics between active drug and placebo were not provided.[171]

Information About TXA From Large Data Sets

We identified a single large surveillance study using the General Practice Database from the United Kingdom.[122] The case-control analysis of deep vein thrombosis reported increased odds of TXA use among cases (OR=3.20; 95% CI, 0.65 to 15.78) and note lack of precision of the estimates based on sparse use of the medication. This report, examining drugs used for heavy menstrual bleeding, found that all common treatments for menorrhagia were associated with deep vein thrombosis risk and raised the question of confounding by indication, meaning that characteristics of the women being treated (abnormal bleeding patterns) rather than the drugs themselves might be the causal component.[122]

Based on United States and worldwide postmarketing reports, the following have been reported in patients receiving TXA for various indications: nausea, vomiting, and diarrhea; allergic skin reactions; anaphylactic shock and anaphylactoid reactions; impaired color vision and other visual disturbances; dizziness; and thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction).[171] There postmarketing reports of venous and arterial thrombotic events included women who had used TXA concomitantly with combined hormonal contraceptives.

In consideration of the information reviewed, the FDA issued contra-indications and precautions for TXA use, advising clinicians not to prescribe TXA to women known to have the following conditions: active thromboembolic disease (e.g., deep vein thrombosis, pulmonary embolism, or cerebral thrombosis); a history of thrombosis or thromboembolism, including retinal vein or artery occlusion; an intrinsic risk of thrombosis or thromboembolism (e.g., thrombogenic valvular disease, thrombogenic cardiac rhythm disease, or hypercoagulopathy). Four precautions are noted: (1) concomitant therapy with tissue plasminogen activators may decrease the efficacy of both medications; (2) the risk of venous thromboembolism and arterial thromboses may increase further when hormonal contraceptives are administered with TXA, of particular concern in women who are obese or smoke cigarettes, especially smokers over 35 years of age; (3) TXA is not recommended for women taking either Factor IX complex concentrates or anti-inhibitor coagulant concentrates because the risk of thrombosis may be increased; (4) patients should be instructed to report visual and ocular symptoms promptly and the medication should be stopped pending a complete ophthalmic evaluation, including dilated retinal examination, to exclude the possibility of retinal venous or arterial occlusion.[171]

Information About TXA From Systematic Reviews

A 2012 review of the efficacy of TXA in treating heavy menstrual bleeding is compatible with this review, finding mild to moderate adverse effects reported in included studies.[173] Gastrointestinal effects were most common, and there were no reports of thromboembolic events in the 10 studies evaluated.[173] A Cochrane review conducted a combined analysis of the efficacy and safety of TXA and ethamsylate as antifibrinolytics used to treat heavy menstrual bleeding; emphasizing the short duration of the included studies, they comment that no increase in adverse events was observed with use of these agents.[174] Two systematic reviews of TXA use in orthopedic surgery recently found no increased risk of thrombotic events in their pooled data

analyses.[175,176] It is important to note that the trials included in these reviews are similar to those in this review in that they are underpowered to detect rare but important harms.

Harms Related to Decision Aids

There are no harms associated with using decision aids other than time invested by patient and clinician if the decision aid does not effectively inform patients about important care options.

Summary

Pharmaceutical agents, procedures and devices, and even diet and exercise have potential complications. While contraceptive methods have typically been well-characterized in the broadly applicable population of reproductive-age women, there may be characteristics associated with abnormal bleeding that modify the risk profile of these interventions when restricted to women with indications related to AUB. Women and their care providers will need to weigh individual risk profiles, desire for contraception, and treatment strategies in order to balance symptom management with minimization of risk, especially when choosing medications that are less well-studied in this population, such as those used for diabetes management.

Discussion

Key Findings

State of the Literature

We identified 1,775 nonduplicate publications through the search process, with 219 proceeding to full-text review (Figure 2). We included 41 publications that reported on 39 separate randomized controlled trials (RCTs) and 12 types of interventions. These studies evaluated the levonorgestrel-releasing intrauterine system (LNG-IUS; 7 studies),[59-65] the contraceptive vaginal ring (1 study),[84] nonsteroidal anti-inflammatory drugs (NSAIDs; 13 studies),[67-70,72-76] tranexamic acid (TXA; 7 studies),[66,71,77-81] combined oral contraceptives (COCs; 6 studies),[50,59,61,68,82,83] metformin (4 studies),[51-54] exenatide (1 study),[53]progestogens (1 study),[49] cabergoline (1 study),[55] acupuncture (2 studies),[57,58] lifestyle/behavioral changes (1 study),[56] and patient decision aids (3 studies)[86,87,177] using at least one comparator or placebo arm.

A number of these studies compared the intervention of primary interest to a progestogen, such as medroxyprogesterone (MPA).[49,60,62,64,70,74,79,80] These studies were not considered important contributions to evidence about the effectiveness of progestogens for treatment since in each case the hypothesis was that the progestogen would be inferior or equivalent to the intervention being studied. Though we report the outcomes for progestogen comparisons to other interventions we have not separately summarized the effectiveness of progestogens. One trial evaluated two routes of progestogen and was treated as a study evaluating progestogen for symptom management.[49]

The quality of the included studies tended to be fair (10 studies)[51,58,60,64,67,75,76,80,81,84] or poor (23 studies).[49,52-54,56,57,59,61-63,65,66,68-71,73,74,77,79,86,87,177] In part, this followed from the difficulty of blinding participants to intervention status. For instance, no LNG-IUS studies included sham insertion or a sham LNG-IUS string placement in the endocervical canal along with placebo medication in both groups, though this would be required to achieve complete masking of intervention groups. Likewise it can be challenging to mask outcome assessors to group status when women and providers assess outcomes. An unmasked participant is counted in the scoring as an unmasked assessor when the outcome is self-reported or self-collected. While this is rigorous and appropriate in the evaluation of risk of bias in RCTs, it may be an inappropriately strict criterion to apply for studies in which menstrual products are collected for measurement of blood loss or in which biological markers such as hemoglobin or hematocrit levels are also assessed. Understanding this context can inform interpretation of the literature.

Effectiveness of Interventions for Abnormal Bleeding

Key Question 1A (KQ1A). Management of Irregular Uterine Bleeding

A number of available interventions suitable for use in primary care have preliminary evidence of effectiveness for improving the regularity of menses. Only metformin has demonstrated effectiveness in more than one RCT with a total of 175 women with polycystic ovaries participating in each of three studies. One study suggests adding exenatide to metformin treatment can enhance effectiveness. No head-to-head comparison trials are available to inform choices among medication types for management of irregular uterine bleeding.

Progestogens

Vaginal micronized progesterone (8% gel) and oral dydrogesterone were studied in a single trial among women clinically classified as having dysfunctional uterine bleeding.[49] In this RCT, both vaginal and oral administration improved cycle regularity with 92 percent and 85 percent of participants, respectively, achieving regular bleeding by the third cycle of use. Effects were comparable, but the trial was not powered to show equivalence or noninferiority.

COCs

A triphasic oral contraceptive was also studied in a single RCT among women with irregular uterine bleeding.[50] This trial included women with both short and long intervals between bleeding episodes and with both heavy and normal amounts of bleeding. The outcomes are provided in aggregate and not presented by initial bleeding characteristics. Overall, 68 percent of women taking the COC achieved excellent or good cycle control compared with 26 percent of those receiving a placebo.

Metformin and Exenatide

Metformin was an active treatment arm in four RCTs conducted among women with polycystic ovarian syndrome (PCOS), two comparing outcomes to a placebo group,[51,52] one comparing metformin with N-acetyl-cysteine,[54] and one comparing metformin only, exenatide only, and both.[53] In each case, metformin was effective for improving the regularity of bleeding over a number of months compared with baseline or placebo. When combined with exenatide the effect was greater than either alone in the study of 60 women with PCOS that compared all three approaches.[53]

Cabergoline

In a very preliminary investigation of this drug indicated for treatment of prolactinomas, cabergoline was associated with return of regular menses in three of eight women in the treated group compared with none of the six receiving placebo.[55] All women in the study had PCOS and normal prolactin levels.

Behavioral and Lifestyle Interventions

Among adolescents with PCOS, both a low-fat, calorie-restricted diet and a carbohydrate-restricted diet in conjunction with 30 minutes of aerobic activity 3 days a week resulted in more regular menses among those who lost weight.[56] This single small study did not present outcomes by the diet group to which participants were randomized. Presumably, there was not a clear difference, meaning there is no evidence to guide choice of dietary intervention. A single trial of acupuncture also included an exercise control group at the same intensity as the diet and exercise trial.[57] This group experienced a 42-percent improvement in regularity of menses. We did not find evidence comparing diet to exercise directly.

Complementary and Alternative Medicine

Two studies of acupuncture with different underlying hypotheses and different methods (conventional acupuncture and low-frequency electroacupuncture) found benefit for a specific style of acupuncture when compared with no intervention or alternate placement of acupuncture needles.[57,58] By 32 weeks in the trial of electroacupuncture for PCOS, women who received acupuncture had a 121-percent improvement in cycle regularity while those who exercised only

had a 42-percent improvement which was statistically comparable in this small trial.[57] Both acupuncture and exercise were superior to placebo in this trial. In the trial of two differing placements of needles, women who received treatment for "mind tranquilizing and menstruation promotion" had greater improvements (no treatment failures among 21 women) compared with those receiving traditional placement (n=16) for "delayed menses" among whom 19 percent did not have improvements.[58]

KQ1B. Management of Abnormal Cyclic Bleeding

The LNG-IUS, various NSAIDs, TXA, and COCs are effective for reducing the amount of menstrual bleeding and in some instances have been shown to have additional benefits. Each category of intervention is described below.

LNG-IUS

All seven studies of the LNG-IUS demonstrated that the intervention effectively reduced heavy menstrual bleeding.[59-65] Evidence suggests the device reduces the volume and duration of bleeding, improves iron status, and is an acceptable alternative to hysterectomy for some women. In direct comparisons, the LNG-IUS was superior to COCs and NSAIDs at reducing menstrual blood loss (MBL). We did not find any studies that compared the LNG-IUS to TXA.

Our analysis of LNG-IUS is consistent with prior systematic reviews. A 2001 systematic review of five RCTs reported mean MBL reductions were between 71 and 96 percent.[178] A 2005 systematic review identified 10 RCTs comparing LNG-IUS with surgery or pharmaceutical treatments.[157] The odds ratio for the proportion unwilling to continue with treatment was 0.27 (95% CI, 0.10 to 0.67) in favor of LNG-IUS. The odds ratio for proportion of women satisfied with treatment was 2.13 (95% CI, 0.62 to 7.33).[157]

Contraceptive Vaginal Ring

One study investigated the contraceptive vaginal ring finding that it was similar in effectiveness to norethisterone when taken orally three times a day for 21 days of each cycle. Overall more women were satisfied with the contraceptive vaginal ring and chose to continue use compared with women taking oral norethisterone.

NSAIDs

In a total of 13 studies, NSAIDs including mefenamic acid, naproxen, meclofenamate, and flurbiprofen, given at the onset of menses for up to 5 days reduce MBL by 20 to 49 percent.[63,66-77] Studies have evaluated use over one to six menstrual cycles. Our analysis of NSAIDs is consistent with a prior 2007 systematic review; NSAIDs were more effective than placebo at reducing bleeding, but less effective than TXA or LNG-IUS.[34] There were no differences in reductions between NSAIDs and oral progestogens, COC, and an older progesterone-impregnated intrauterine system (Progestasert®). There were no differences seen between individual types of NSAIDs, specifically mefenamic acid and naproxen. The most recent study found similar reductions in pictorial blood loss assessment chart scores when NSAIDs were combined with TXA compared with TXA alone. NSAIDs reduce MBL, but do not consistently reduce MBL to clinically meaningful levels (i.e., less than 80 ml) in all patients. There was considerable variability in response. Some patients had an increase in blood loss during treatment. NSAIDs do not regulate the pattern of menstruation nor provide contraception. NSAIDs do provide relief of dysmenorrhea. Therefore, for patients who desire both reduced

MBL and relief from dysmenorrhea, but not contraception, and who do not have contraindications, NSAIDs can be considered for up to five days during menses.

TXA

All seven RCTs of TXA demonstrate effectiveness of improving heavy bleeding.[66,71,77-81] TXA at a dose of 1.95 to 4.5 grams per day for 4 to 5 days from onset of bleeding meaningfully reduces MBL by 40 to 60 percent in studies lasting up to 1 year. Both biologic and self-reported symptoms of bleeding severity are improved. Our analysis of TXA is consistent with prior systematic reviews of another formulation of TXA. A 1995 systematic review pooled results from seven trials and found a reduction in MBL of 46.7 percent (95% CI, 47.9% to 51.6%) with TXA.[179] A 2004 systematic review and meta-analysis of two RCTs of TXA versus placebo reported a mean MBL difference of −93.96 ml (95% CI, −151.43 ml to −36.49 ml) in favor of TXA treatment.[174]

COCs

Though the volume of RCT literature examining use of COCs in women with abnormal uterine bleeding (AUB) is somewhat small relative to the frequency with which these agents are used as a first-line therapy in women presenting with AUB symptoms, our analysis indicates these agents are associated with decreases in AUB among treated women. All five RCTs of COCs for the indication of heavy cyclic menstrual bleeding found benefit for reducing volume of menstrual bleeding. [59,61,68,82,83] Two studies also identified improvements in related laboratory values such as hematocrit and ferritin, [82,83] and one study also found significant improvement in patient rating of overall health.[59] These findings are consistent with the 2010 American Congress of Obstetrics and Gynecology recommendations, which note that combined hormonal contraceptives are a "reasonable option for initial management of menorrhagia."[21] In the two head-to-head comparisons between COCs and LNG-IUS,[59,61] reductions in heavy menstrual bleeding were documented in both treatment groups, with a somewhat greater benefit for LNG-IUS users.

Decision Aids

Three studies investigated decisions aids to assist women seeking treatment for heavy cyclic bleeding in making informed decisions about care.[86,87,177] The study results suggest that decision aids increase patient knowledge and enhance satisfaction with care but do not affect disease symptoms in directly measureable ways. One study found fewer women who received the decision aid ultimately chose surgical referral and hysterectomy.[86] However this decision cannot be linked to improvement in bleeding symptoms. Since there are no known harms associated with using decision aids, they may help patients evaluate treatment options and feel secure in their choices.

Applicability

Applicability describes the extent to which results observed in published studies from this this review are likely to reflect the expected outcomes when an intervention is applied to broader populations in real-world conditions. Studies for this review were intended to provide information to inform primary care management of AUB, whether irregular or cyclic. In shaping the methods for this review, we have engineered the report so that the included research is applicable to primary care of women in the United States. Our stricter criteria, narrowing

findings to only symptomatic populations of reproductive-age women with chronic complaints of abnormal bleeding, comes at the cost of fewer studies being addressed. However, it assures that those studies that are included were explicitly designed to examine the effectiveness of the treatments for improving the outcomes of interest in the populations of interest. Applicability of the findings is therefore high.

For each intervention, it is important to note the following provisions. The results of this review apply for women:

- Who are reproductive age and state they have an irregular pattern of menstrual bleeding or heavy cyclic menstrual bleeding.
- Without abnormal findings on pelvic exam or on ultrasound report (fibroids, polyps).
- Without an intrauterine device (IUD) in place, and who are not pregnant or lactating,
- Who are healthy, and without renal impairment, hepatic impairment, intestinal disease, thyroid disease, abnormal cervical cytology, noncyclic bleeding, history or presence of significant medical problems (e.g., thromboembolic disease, coagulopathy, subarachnoid hemorrhage, endocrine disorders, or eye disease).
- For whom any additional clinically determined diagnostic and screening tests have be completed to rule out these and other causes of abnormal bleeding.
- Does not have any of the contraindications found in the Food and Drug Administration sources discussed in the main document and do not have risks of drug-drug interactions if they take multiple prescription medications.

Our review was not designed to guide evaluation of women with abnormal bleeding, rather to address what treatments have evidence of effectiveness once the diagnosis is established and primary care management is to be initiated.

Applicability of Literature About Interventions for Irregular Uterine Bleeding (KQ1A)

The literature about management of irregular uterine bleeding applies to women in primary care settings in the United States. Ten RCTs, three conducted in the United States, two in Italy, two in Turkey, and one each in China, Sweden, and the United Kingdom provide evidence about seven types of intervention. Enrolled populations were narrowly defined and had either a clinical diagnosis of irregular uterine bleeding, or met research criteria for PCOS. As a result the findings are strictly applicable only to these groups of women. We describe the agents study within the two populations in which the research was conducted.

Use for Irregular Uterine Bleeding (KQ1A)

Progestogens

The study comparing vaginal micronized progesterone (8% gel) with oral dydrogesterone for a 10-day time period is applicable to primary care in the United States, as both routes are used in standard care in the United States to provide progesterone in order to organize a withdrawal bleed that will typically occur within days of completing the progestogen. The oral agent in this trial, dydrogesterone, is not available in the United States. This study is therefore a surrogate for oral versus vaginal administration of similar progestogen formulations such as MPA that are widely used in the United States for this purpose; however it does not provide direct evidence to support use of other agents. The outcome of interest for this review was regularity of bleeding after treatment which was provided for three menstrual cycles. Both groups had improvement

however applicability for chronic use is unclear as no long-term followup of symptom control is available. Progesterone is often used in management of specific causes of abnormal bleeding such as PCOS however this study does not directly apply because the population was not addressed in this study. Progesterone can be used by women who wish to conceive.

COCs

The single study, conducted in the United States, is directly applicable to primary care in the United States. The study population of 201 women is representative of the spectrum of complaints that may accompany chronic irregular uterine bleeding including menses that are widely separated in time whether light, normal, or heavy with regard to heaviness of bleeding, and includes women with closely space and unpredictable bleeding also without restriction on heaviness of bleeding. The intervention is a common version of triphasic COC (Ortho Tri-Cyclen®) that provides direct evidence for its effectiveness and indirect evidence for other triphasic pills with similar dosing profiles. The evidence is less direct but likely applicable to monophasic pills of similar estrogen and progestogen content. It does not apply to progestogen-only formulations or to pills with estrogen doses lower than 0.035 mcg as used in this study. Comparison to placebo provides definitive evidence of benefit but does not provide information about how COCs compare to other strategies that might be used such as LNG-IUS or progestogens. The outcomes included those that are a priority of women seeking treatment for uterine bleeding and included cycle regularity, incidence of excessive bleeding, and overall rating of symptom improvement.[50] Harms and contraindications, as discussed in KQ2, are well-known to care providers and often to women themselves, and COCs are not applicable as a long-term strategy for women who wish to conceive.

Management of PCOS (KQ1A)

Metformin and Exenatide

The four trials that investigated use of metformin are applicable to care in the United States and were conducted in the United States, Turkey, Italy, and the United Kingdom. The study in the United States compared metformin, to exenatide or both. These studies enrolled women with PCOS and fewer than expected normal menses. They investigated doses of metformin that are available in the United States (500 mg and 850 mg, administered by mouth twice daily). None of the studies used an extended-release form which is now available so evidence related to that formulation is indirect. The outcome of interest for this review was menstrual frequency which was improved compared with placebo in 2 trials. One head-to-head comparison was metformin compared with exenatide or both. Both were superior to either alone for cycle control. Another trial compared metformin to N-acetyl-cysteine. The most common side effect which is gastrointestinal symptoms was identified in these studies and thus would be expected to apply to this typically younger group of women who do not have diabetes. Metformin can be used by women who wish to conceive and is safe for use in pregnancy. Based on other literature, it may enhance fertility. Little is known about exenatide and fertility and safety in pregnancy, however it does not have contraceptive effects.

Diet and Exercise

The applicability of the single trial of diet and exercise is limited. It enrolled 24 adolescents with PCOS, 16 of whom completed the study and evaluated a low-fat, calorie-restricted diet or a carbohydrate-restricted diet along with 30 minutes of anaerobic exercise 3 days a week. The trial

did not provide an intention to treat analysis, comparing arms but did report that weight loss in either group improved cycle regularity. Behavioral changes can be applied in many populations and would be expected to have benefits. Thus evidence is insufficient to advise which dietary pattern is superior. Another arm of a single study found exercise 30 minutes each day, 3 days a week, was more effective than no intervention and as effective as acupuncture in improving cycle regularity.

Acupuncture

Two trials, one conducted in Sweden and one in China, assessed acupuncture. Depending on the availability and the skill of acupuncturists available in communities, this intervention may not be broadly applicable in the United States. Both tradition acupuncture and electroacupuncture improved cycle regularity but this was assessed in essentially unblended trials. The outcomes examined were relevant to patient symptoms however were very poorly-described in one study in which the investigators applied categories like "cured" without clear definitions. Overall, literature is absent to inform choice of any of these modalities over another.

Applicability of Literature to Management of Abnormal Cyclic Bleeding (KQ1B)

Twenty-nine studies contributed evidence about interventions for management of abnormal cyclic bleeding focused predominantly on effectiveness for reducing the amount of bleeding among women with heavy menstrual bleeding. Overall these RCTs are applicable to primary care in the United States. Five were conducted in the United States (including two multi-country trials), eight studies were conducted in the United Kingdom, four studies were conducted in Canada (including two multicenter studies), three studies were conducted in Australia (including one multicenter trial), and two each were conducted in Finland, Egypt, and India. A single study was conducted in each of the following countries: Netherlands, Sweden, and Turkey.

LNG-IUS

Overall, the study findings for LNG-IUS from this review apply to women in the primary care settings in the United States. One trial was conducted in three countries (United States, Canada, and Brazil), two trials were conducted in the United Kingdom, and the others were conducted in Egypt, Canada, Turkey, and Finland. The settings are not substantially different from a primary care setting in the United States. However, a limitation is that adolescent women and women with obesity were not included in the RCTs populations, so direct applicability to their care is lacking. Enrolled populations met our inclusion criteria and like others used direct measures of volume of bleeding that would be replaced in clinical care with patient self-report.

The LNG-IUS is available in the United States. The intervention dosage was the same for all seven trials and is that currently marketed (52 mg levonorgestrel, initial release rate 20 mcg per 24 hours). The LNG-IUS must be inserted by a provider. The details of the insertion procedure must be understood and practiced to safely provide this treatment in a primary care setting. The comparator differed among the seven trials; two trials compared LNG-IUS to a COC, three trials compared LNG-IUS to a progestogen (oral or intramuscular route), one trial used an NSAID as a comparator, and one trial assigned the patients in the control group to continue with their existing medical treatment for excessive uterine bleeding or symptoms of dysmenorrhea, or both. None of the trials compared LNG-IUS with TXA.

The primary outcome of the trials was change in blood loss which directly addresses the primary symptom for which women typically seek treatment. One study used the proportion of women who cancelled their prior decision to undergo hysterectomy as the primary outcome measure. Timing of assessment of outcome varied among the trials: one trial reported after 1 menstrual cycle, three trials reported after 3 menstrual cycles, four trials reported after 6 menstrual cycles, and two trials reported after 12 months. The latter are more informative for a device intended to be in place for 5 years.

Contraceptive Vaginal Ring

The contraceptive vaginal ring is available in the United States, and the group of women enrolled in the only study available is comparable in symptom profile to those in other studies in this CER. MBL reduction between the contraceptive vaginal ring users and the comparison group receiving norethisterone 3 times daily was similar. Women in the contraceptive vaginal ring group were more satisfied with treatment, however, it is important to note that comparison of the ring to an agent dosed 3 times each day may not be applicable to typical practice patterns in the United States when selecting a progestogen to prescribe for AUB.

NSAIDs

The 13 RCTs examining NSAIDs and included in this review are applicable to United States populations. The studies were conducted in seven countries including Australia (2 studies), Canada (1 study), India (2 studies), the Netherlands (1 study), Sweden (1 study), the United Kingdom (5 studies), and the United States (1 study). In some trials, women were excluded who were on hormonal medications, had menorrhagia related to an IUD, or who were taking NSAIDs or steroids. Therefore, results of these studies are applicable to women with no contraindications to NSAIDs including underlying hepatic, renal, or thyroid disease, stomach ulcers, or asthma, and no drug sensitivity.

The specific NSAID administered to participants varied and included mefenamic acid (11 trials), naproxen (2 trials), flurbiprofen (1 trial), and meclofenamate (1 trial). One trial evaluated mefenamic acid in conjunction with TXA. For each NSAID, dose and duration did not vary greatly, with usually up to 5 days duration of use. The most commonly used dose of mefenamic acid was 500 mg 3 times a day starting at the onset of menses. One trial initiated mefenamic acid 5 days prior to onset of menses through cessation of bleeding. Another trial used 500 mg at onset of menses followed by 250 mg every 6 hours for 3 to 5 days. Mefenamic acid at a dose of 250 mg 3 times a day from onset menses for 5 days was used when combined with TXA in one trial. Naproxen was evaluated with initial loading doses of 500 to 550 mg then 250 to 275 mg every 6 hours for 5 days or until 24 hours after cessation of heavy bleeding. Meclofenamate was studied at a dose of 100 mg 3 times a day from onset of menses for duration of 6 days or until cessation. Flurbiprofen was studied at a dose of 100 mg twice a day from onset of menses for duration of 5 days. Each of these doses is available for prescription in the United States. Notably, the literature lacks RCTs about ibuprofen which is likely the most common prescription and over-the-counter NSAID used for heavy bleeding and dysmenorrhea.

Outcomes for the trials in this review included documentation of objective blood loss. This is not applicable in routine clinical care and subjective assessment of MBL is nearly always used as the criteria for initiating and determining success with NSAIDs. NSAIDs are also effective in reducing dysmenorrhea, and therefore patients with both heavy cyclic menstrual bleeding and dysmenorrhea or headaches may desire NSAIDs.

TXA

The literature about TXA for management of abnormal cyclic bleeding applies well to women in primary care settings in the United States. Two trials were conducted in the United States, three were conducted in Europe, and one took place in India. Enrolled populations met inclusion criteria and reviewed studies implemented exclusion of participants as described in the methods for this review. Because women with comorbidities are systematically excluded from these trials, we must note the studies apply to healthy women with heavy cyclic menstrual bleeding. While studies quantified the amount of bleeding at baseline, this is typically not feasible in clinical populations and the patient's statement that menstrual bleeding is heavy would be more likely to be used as a criterion for consideration of this therapy.

The formulation of TXA (Lysteda®) used in the included studies is the same that is currently available in the United States. The intervention dosage differed among the five trials but was in the range of 1.95 to 4.5 grams per day for 4 to 5 days. Treatments compared with TXA in these trials did not include LNG-IUS or COC regimens. This modestly limits applicability since these would be among the usual interventions considered in real-world clinical settings.

The primary outcome of the TXA trials was change in blood loss which is typically the most pertinent symptom for women. The timing of assessments of outcomes varied among the trials but was generally short: two trials reported after two menstrual cycles, four trials reported after three menstrual cycles, one trial reported after six menstrual cycles. No trials reported outcomes for use of TXA for 1 year or more of therapy. This limits understanding of applicability for long-term use of this agent. Reporting of adverse events was not adequate for an assessment of harms and in the context of short followup in trials, this prevents consideration of risks.

COCs

The findings of this review are applicable to women visiting a primary care setting for management of heavy, cyclic uterine bleeding. The included RCTs were conducted in the United States (1 study), Canada (2 studies), Australia (1 study), multiple sites in Europe (1 study), and Egypt (1 study) in outpatient clinical care settings. Known contraindications to use of COCs and abnormal findings during diagnostic work-up (e.g., fibroids or other endometrial pathology) were commonly employed as exclusion criteria in the identified studies and these diagnostic exclusions are applicable in the general primary care setting as well. Study participants were all older than 18, and had normal range body weights so no evidence directly informs symptom management or safety in younger adolescents or obese patients. COCs were compared with placebo in three studies and with LNG-IUS in two studies. Both participants in the COC group and LNG-IUS had improvements from baseline, but the LNG-IUS was superior to COC. In comparison to mefenamic acid, COCs were superior. The outcomes assessed were those of high relevance to patients and included MBL, blood counts and iron reserves, and participant and clinician assessment of symptoms.

Decision Aids

Use of decision aids is increasingly common and promoted in U.S. health care settings especially in clinical contexts in which patient preference plays a strong role in selection of the treatment and prioritization of outcomes. Three studies of decision aids are included in this review. Two were conducted in the United Kingdom and one in Finland. They are somewhat applicable to care in the United States but may not directly apply given differences in payment structures for care and prescriptions as well as potential differences in clinical care norms. All

three studies used information booklets mailed to patients prior to their appointments and one added a computerized decision tool. The studies assessed outcomes like general health status, quality of life, and decisional conflict, as well as secondary outcomes like anxiety. Study populations included women older than 30 and 35 respectively in the two that reported, so findings do not generalize to younger women. None found benefit which may or may not reflect how similar approaches would be received in a U.S. health care context or across a broader age span of women.

Final Comments on Applicability

Overall applicability of this literature to providing care was high. However, often women who are in trials do not reflect the full range of those with abnormal bleeding seen in primary care and, as we have noted, groupings of participants do not correspond directly to newer classifications of sub-types of AUB.[9] Study participants were more likely to be normal weight, nonsmokers, with few, if any concomitant conditions. The interventions (except in the case of specific comparators as noted) are available in the same doses and formulation in the United States. Outcomes such as measured blood loss, self-reported symptom severity and days of bleeding are of direct relevance to women with abnormal bleeding. Our findings are sparse for outcomes which can be considered essential for a condition like AUB that are defined by symptoms. Important outcomes include satisfaction with response to treatment, definitive assessments of whether or not the women considered their complaint resolved, and whether they wished to continue the same treatment or add additional treatments. Followup in general was brief, so they findings may not apply well to management of a chronic condition like abnormal bleedings. This makes findings about assessments of harms challenging since use of interventions over extended periods may have different risk profiles from short timeframes like one to six cycles.

Summary of Strength of Evidence and Findings

Overall the evidence to answer KQs about the management of AUB, did not reach standards for high strength of evidence for any intervention. This was particularly true in the literature relevant to treatment of women with irregular uterine bleeding. Combined oral contraceptives, as represented in a single good quality placebo controlled trial with a total of 201 participants, documented effectiveness. The treatment effect was large with improvement in bleeding patterns reported for more than 80 percent of women taking COC compared with 45 percent for the placebo group. Combined, these factors provided moderate evidence of benefit. Use of metformin is supported by low strength of evidence predominantly related to small trials with somewhat limited quality. For the remainder of the interventions investigated for management of irregular uterine bleeding, there is insufficient evidence that follows from single or lower quality studies, or both.

The strength of evidence tables (Table 22 and Table 23) that follow summarize the total number of studies and within those studies the number of women who received the specific intervention. The tables also provide the assessment of the risk of bias, consistency of findings across trials, directness of the evidence that treatment improves the symptom, and precision of the estimated provided by the literature. The complete scoring is found in the Appendix J. For KQ1B, risk of bias associated with blinding of patients, personnel and outcome assessment was most likely to compromise overall assessment of study quality. For KQ1A, risk of bias

associated with blinding of patients and personnel and incomplete outcome data was most likely to compromise overall study quality.

Table 22. Strength of evidence for improving menstrual regularity (KQ1A)

Intervention Quality: Studies (Subjects Assigned to Intervention)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence[a]	Findings Comparisons
Progestogen[b] Poor: 1(69)[49]	High	NA	Direct	Imprecise	Insufficient	Not analyzed by arm
COC[c] Good: 1(101)[50]	Low	NA	Direct	Precise	Moderate	Cycle control improved:[d] 87% COC vs. PBO, p<0.001[50]
Metformin[e] Poor: 3(81)[52,53,54] Fair: 1(45)[51]	Medium	NA	Direct	Imprecise	Low	Delay to first ovulation:[f] 24 days MET vs. PBO, p=0.02[51]
Exenatide[g] Poor: 1(20)[53]	High	NA	Direct	Imprecise	Insufficient	Small, poor quality trial
Cabergoline[h] Good: 1(8)[55]	Low	NA	Direct	Imprecise	Insufficient	Cycle control improved:[i] 100% CBG vs. PBO, p=NR[55]
Diet[j] Poor: 1(24)[56]	High	NA	Direct	Imprecise	Insufficient	Not analyzed by arm
Exercise[k] Poor: 1(34)[57]	High	NA	Direct	Imprecise	Insufficient	Not analyzed by arm
Acupuncture[l] Poor: 1(33)[57] Fair: 1(23)[58]	High	NA	Direct	Imprecise	Insufficient	Menstrual regulation:[m] 86% MP-ACU > R-ACU, p<0.05[58]

CBG = cabergoline; COC = combined oral contraceptive; MET = metformin; MR-ACU = menstruation-promoting acupuncture; NR = not reported; PBO = placebo; R-ACU = routine acupuncture

[a]Overall strength of evidence assessment based on good and fair quality studies only.

[b]Oral dydrogesterone (n=35) vs. 8% vaginal micronized progesterone (n=34).

[c]Triphasic norgestimate-ethinyl estradiol vs. placebo (n=100).

[d]Subject assessment.

[e]Poor quality studies: metformin vs. N-acetyl cysteine (n=50), exenatide (n=20), or placebo (n=12); Fair quality study: metformin vs. placebo (n=47).

[f]Mean days to ovulation.

[g]Compared with metformin (n=20) or metformin plus exenatide (n=20).

[h]Compared with placebo (n=6).

[i]Menstrual cyclicity restoration in oligomenorrhea or spontaneous menses in amenorrhea.

[j]Low-fat diet (n=12) vs. low-carbohydrate diet (n=12).

[k]Compared with acupuncture (n=33) or no intervention (n=17).

[l]Poor quality study: acupuncture vs. exercise (n=34) or no intervention (n=17); Fair quality study: mind tranquilizing acupuncture vs. routine acupuncture (n=17).

[m]Patients cured or markedly relieved.

For management of heavy cyclic bleeding the literature was more robust. Combined oral contraceptives are supported by high strength of evidence for the purpose of decreasing MBL. The LNG-IUS, various NSAIDs, and TXA are also effective for reducing the amount of measured menstrual bleeding and are each supported by moderate strength of evidence. Of note, in head-to-head comparisons with statistically significant differences, the LNG-IUS has one trial each showing superiority to NSAIDs, two showing superiority to COCs, and two showing

superiority to progestogens. COCs were superior in one trial compared with an NSAID. TXA was also superior to an NSAID, and when combined with an NSAID was superior to TXA alone. Most of these interventions have been shown to have additional positive effects, typically including shorter duration of bleeding and improvement is symptoms when participants used standardized scoring systems to report on treatment response.

Table 23. Strength of evidence for improving heavy menstrual bleeding (KQ1B)

Intervention Quality: Studies (Subjects Assigned to Intervention)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence[a]	Findings[b] Comparisons
LNG-IUS Poor: 5(173)[59,61-63,65] Fair: 2(104)[60,64]	Medium	Consistent	Direct	Precise	Moderate	71% and 94% reduction in MBL in 2 head-to-head studies LNG-IUS > MPA, p<0.001[60] LNG-IUS vs. NOR, p=NS[64]
NSAID Poor: 9(192)[63,66,68-71,73,74,77] Fair: 3(113)[67,75,76,93] Good: 1(32)[72]	Medium	Consistent	Direct	Imprecise	Moderate	28% to 49% reduction in MBL in 3 placebo controlled trials; 46% and 47% reduction in MBL in 1 head-to-head study (2 NSAID arms) MFA vs. PBO, p=NR[67] p<0.001[76,72] MFA vs. NPX, p=NS[75]
TXA Poor: 4(202)[66,71,77,79] Fair: 2(260)[80,81] Good: 1(123)[78]	Medium	Consistent	Direct	Precise	Moderate	26% and 40% reduction in MBL in 2 placebo controlled trials; 45% reduction in MBL in 1 head-to-head study TXA vs. PBO, p<0.001[81,78] TXA > NOR, p<0.001[80]
COC[c] Poor: 3(90)[59,61,68] Good: 2(269)[82,83]	Low	Consistent	Direct	Precise	High	64% and 69% reduction in MBL in 2 placebo controlled trials COC vs. PBO, p<0.001[83,82]

Table 23. Strength of evidence for improving heavy menstrual bleeding (KQ1B) (continued)

Intervention Quality: Studies (Subjects Assigned to Intervention)	Risk of Bias	Consistency	Directness	Precision	Overall Strength of Evidence[a]	Findings[b] Comparisons
Progestogen[d] Poor: 4(161)[79,62,70,74] Fair: 4(173)[60,64,80,84]	Medium	Inconsistent	Direct	Imprecise	Insufficient	20% increase to 87% reduction in MBL in 4 head-to-head studies MPA < LNG-IUS, p<0.001[60] NOR < LNG-IUS, p=NS[64] NOR < TXA, p<0.0001[80] NOR vs. CVR, p=NS[84e]
CVR Fair: 1(48)[84]	Medium	NA	Direct	Imprecise	Insufficient	67% reduction in MBL[e] in 1 head-to-head study CVR vs. NOR, p=NS[84]

COC = combined oral contraceptive; CVR = contraceptive vaginal ring; LNG-IUS = levonorgestrel-releasing intrauterine system; MBL = menstrual blood loss; MCF = meclofenamate; MFA = mefenamic acid; MPA = medroxyprogesterone; NA = not applicable; NOR = norethisterone; NPX = naproxen; NR = not reported; NS = not significant; NSAID = nonsteroidal anti-inflammatory drug; PBO = placebo; TXA = tranexamic acid

[a]Overall strength of evidence assessment based on good and fair quality studies only.

[b]Change in menstrual blood loss from baseline measured by the alkaline hematin method (unless otherwise noted) from good and fair quality studies.

[c]thinyl estradiol and levonorgestrel (n=71) or norethindrone and ethinyl estradiol (n=19) or estradiol valerate and dienogest (n=269).

[d]Medroxyprogesterone (n=177) or oral norethisterone (n=113) or depot medroxyprogesterone (n=44).

[e]Percent change in menstrual blood loss measured by the pictorial blood loss assessment chart.

Implications for Clinical and Policy Decisionmaking

This review highlights the variety of options that can be effective for management of abnormal bleeding. We hope it serves to encourage care providers and women to consider the full range of potentially helpful interventions. This review may help to underscore the fact that contraceptive options like LNG-IUS and COCs are a proven option, while widening consideration to include agents like metformin for women with PCOS and TXA for those with heavy bleeding. Clinicians may be also be alerted to the some of the constraints of the literature for these specific populations and proceed with more information to guide decisions and to discuss likely side effects and potential harms.

Since these conditions are not typically life-threatening but are chronic, problematic, and can be embarrassing and costly in terms of lost productivity, the primary health system and policy challenge is to recognize that failure to address AUB is unnecessarily diminishing women's quality of life and function.[1,8] Cost differences are unlikely to drive choices among many of these interventions, though initial costs of long term treatments like the IUS can be disincentives if up-front or maintenance costs to the patient are high.[180-183] Likewise for newer drugs, like TXA, decisions about eligibility and copays could influence uptake and continued utilization of an effective medication. All the interventions described, with the exception of exenatide, cabergoline, and acupuncture, are likely to be covered by most payors for these indications. For the treatments noted that have not yet proven effectiveness in large well-conducted studies this will need to be addressed with high quality research before policy decisions can be recommended.

Limitations of This CER

In this review we focused tightly on primary care interventions for two specific patterns of abnormal bleeding (irregular and cyclic). While this approach was identified by our team, Key Informants, and the Technical Expert Panel (TEP) as an area of the literature that would benefit from evidence synthesis, our focus does prevent comparison to second line therapies that may be used by subspecialists for women who have failed primary care treatment and prevents examination of how these medications fare when compared with surgical options. The latter category of study is fairly small, and for broader perspective, there are a number of reviews within the last 5 to 10 years that provide more sweeping information about these interventions. For the reader's convenience, Appendix M lists these reviews and related practice guidelines and summarizes the conclusions that are relevant to the focus of this review.

Existing literature cannot uniformly be related to more recent updates in classification of AUB that have potential to drive greater uniformity in research and greater thoroughness in clinical evaluation. At present the inclusion and exclusion criteria of trials, the operational definitions of the condition under study and the level of screening of participants to document conformity with the FIGO 2011 classifications is lacking. As a result this literature synthesis is constrained to groupings that are less specific. Nonetheless we have organized the findings into groupings that are clinically recognized presentations and this evidence does apply for the scenarios described.

We restricted this review to publications in English. Based on review of abstracts (generally available in English) and on the expertise of our team and TEP, we do not feel that this biases the review for assessment of the LNG-IUS and medications because few studies were omitted, and larger, higher quality trials are typically published in the English language literature. The sole domain that may be fundamentally under-represented because of this strategy is complementary and alternative medicine which includes interventions such as herbal remedies, acupuncture, and massage therapy. We also restricted interventions to those that had been studied in randomized trials. This limits the degree of context that we can provide from observational studies about factors such as predictors of treatment success or effect modifiers. However, it is uncommon for observational studies to meet criteria sufficient to influence the assessment of strength of evidence when there are trials available, so this restriction is unlikely to have influenced the overall findings of this review.

Limitations of the Evidence Base

Throughout the report we endeavored to point out limitations specific to the included populations, comparisons, and quality of the literature. Recent improvements in unifying nomenclature and formalizing consensus definitions for the clinical groupings of bleeding abnormalities[9] will likely continue to have a positive influence on the ability to properly interpret the findings of individual studies, to identify groups of studies with comparable methods and to aggregate results. Though we did not systematically review literature about pathophysiology, normative patterns for bleeding, natural history of AUB subtypes, or health systems influences, we comment here beyond the need for specific trials in order to encompass other forms of research that could enhance the design and conduct of effectiveness studies as well as filling important gaps in knowledge that hinder research.

Methodologic Limitations

Recurring methodologic recommendations include a need for:

- Larger RCTs, appropriately powered for direct head-to-head comparisons of treatment options in which loss of participants is minimized and intention-to-treat analyses are uniformly conducted.
- Detailed attention to operational criteria for defining the bleeding pattern under study and for methods used to define inclusion and exclusion. Conformity with FIGO PALM-COIEN sub-types may be desirable.
- Study of the validity and reproducibility of classification of women presenting with problem irregular and cyclic bleeding using the PALM-COIEN groupings or other approaches is needed to understand the diagnostic properties of clinical classification systems.
- Clear and definitive operational definitions of outcomes that include, indeed prioritize, patient-reported, condition-specific quality of life and satisfaction measures over durations of time compatible with treatment of a chronic condition. This should include assessments of whether the woman herself considers her bleeding problem resolved.
- Study populations that match the characteristics of those who present with AUB in primary care settings. This includes teens, perimenopausal women, heavier women, and women with common comorbidities such as diabetes and hypertension.
- More effective mechanisms of masking participants, researchers, and providers to intervention status. This may include need to develop sham procedures to mimic IUD insertion and to provide a sham "string" to confirm placement should a patient or provider check status. (Of note the IUD is effective without a string and string-less insertion is also an option for research where placement can be confirmed by ultrasound.)
- Studies designed to assess treatment trajectory and cost. Such studies could randomize women to distinct treatment pathways and track the rate of conversion from one treatment to another for inadequate symptom control or sequence addition of measures, so that the effectiveness of combining multiple intervention methods can be assessed.
- An overall shift towards effectiveness from efficacy, moving beyond the level of proof of concept that is required for drug and device approval to a deeper level that can better inform care, cost considerations, and policy.

Ongoing Research

We identified four ongoing studies that may add to our understanding of the relative safety and efficacy of different regimens for treatment of AUB (additional details provided in Appendix P). Two currently funded trials are exploring the effect of a pretreatment regimen, one employing misoprostol and one using norethindrone acetate, on short and long term bleeding outcomes among women undergoing placement of an LNG-IUS for treatment of heavy menstrual bleeding. A large postmarketing surveillance study of the Mirena® LNG-IUS is also underway in Kazakhstan, with a planned enrollment of 1,700 participants, potentially contributing additional safety information to this body of literature. The utility and safety of new investigational agent, a selective progesterone receptor modulator (CDB-2914) that has shown promise for reducing bleeding in studies involving women with fibroids, is also currently being assessed in a study involving women with AUB.

Future Research Needs

While the number of informative studies that could be designed is likely limitless, we list examples, grouped by indication and intervention, of types of studies that could resolve current and pressing gaps in knowledge.

Irregular Uterine Bleeding

- Development of a body of literature that examines benefits of exercise and weight loss focused on improving bleeding patterns in women with irregular bleeding that results from failed, mistimed, or poor-quality ovulation.
- Continued investigation of the role that insulin sensitizing and glycemic control agents like metformin and exenatide have on improving irregular bleeding patterns.
- Carefully controlled trials of complementary and alternative medicine interventions like acupuncture for improving menstrual regularity.
- RCTs specifically designed to assess both the heaviness and the interval of bleeding in women with irregular bleeding, which could include approaches shown to have benefit for heavy cyclic bleeding.

Abnormal Cyclic Uterine Bleeding

- Investigate the epidemiology and natural history of heavy menstrual bleeding in representative primary care populations in order to better understand the boundaries of what constitutes normal bleeding patterns and to document the trajectory of AUB. This would for instance, contribute data about what factors predict severity and whether a proportion of cases are self-limited.
- Determine whether harms reported to be associated with treatments for heavy bleeding result because a causal contributor to the heavy bleeding is also related to the harm. For instance abnormalities in coagulation may enhance risk of DVT and be associated with heavy menses. Analyses for such confounding by indication may better assess risk of harms and predictors of response.
- Across specific interventions, additional research and analysis is needed to determine which individuals are most likely to respond to which interventions. This could develop from personalized medicine approaches, from better understanding of the mechanisms underpinning AUB, or from predictive modeling in large datasets.
- Assess the acceptability and cost-effectiveness of various treatments in the primary care setting in the United States including LNG-IUS, NSAID, COCs and TXA.
- Determine the most valid and accurate indirect measures of MBL that can be used in primary care settings and that correlate with objective direct measures.

Progesterone Containing IUDs Including the LNG-IUS

- Establish a registry of LNG-IUS users in the United States for extended followup of potential harms and preventive effects (e.g., reduced risk of endometrial cancer, anemia).
- Extend postmarketing surveillance to assure safety when used in teens and nulliparous patients.
- Examine costs in light of whether the treatment simultaneously resolves bleeding complaints and provides contraception.

NSAIDs

- Directly compare classes of NSAIDs including commonly available over-the-counter preparations.
- Conduct long-term effectiveness studies to determine if treatment effects are durable or wane over time.
- Model the costs of treatment with varied NSAID dosing strategies.
- Determine if "pre-loading" in the days before onset of menses significantly reduces menstrual bleeding alone and in combination with NSAIDs after onset of menstrual bleeding.

COCs

- Conduct direct comparisons of COCs with other AUB management strategies to better understand the relative merits of treatment options.
- Examine costs in light of whether the treatment simultaneously treats complaints and provides contraception.

TXA

- Establish a registry of TXA users and exploit existing large payer datasets to examine long-term followup for both effectiveness beyond 6 months and incidence of rare/uncommon adverse effects.

Conclusions

Women who have problematic irregular or heavy cyclic menstrual bleeding have a number of treatment options available that are supported by systematic review of the research literature. These include high strength of evidence that COCs can improve menstrual regularity for women with irregular bleeding patterns. Metformin is supported by moderate strength of evidence for improving cycle regularity especially among women with PCOS. This provides both a contraceptive and a noncontraceptive option for irregular menses. Other interventions like progestogens are associated with statistically and clinically meaningful improvements from baseline patterns, however the overall evidence is insufficient from well-designed, larger studies with ability to directly compare treatment arms rather than only pre-post measures within groups.

Multiple interventions for heavy cyclic bleeding are supported by evidence that they reduce MBL. These include strong evidence that COCs are effective and moderate strength of evidence that LNG-IUS, NSAIDs, and TXA reduce bleeding relative to baseline, decrease total volume of bleeding when comparisons are made across treatment groups, and when measured, decrease days of bleeding. In direct comparisons, LNG-IUS is superior to NSAIDs. TXA is superior to NSAIDs and TXA combined with an NSAID was superior to TXA alone. Results from COC and NSAID comparisons suggest comparable effectiveness. Not all women who are treated with any of these interventions that can be effective will improve. Across agents data are sparse to evaluate long-term improvements and risk of harms.

Limitations include a predominance of small, short trials lacking standard terminology and diagnostic criteria for identifying and including women with AUB. Tools for collecting outcome data are crude (collection of sanitary products) and may contribute to a high rate of attrition. Biologic outcomes, like measured blood loss and hemoglobin or hematocrit levels, may neglect the importance of patient-reported outcomes that assess whether symptoms are considered

resolved by women themselves. Nevertheless, the variety of effective options suggests many women can achieve symptom relief and will have available to them choices that address both symptoms and contraceptive or fertility desires, as well as potentially improving other symptoms like menstrual cramping.

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Abbreviations and Acronyms

ARHQ	Agency for Healthcare Research and Quality
CER	Comparative Effectiveness Review
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COC	Combined oral contraceptive
g	Gram
GnRH	Gonadotropin-releasing Hormone
HRQoL-4	Health related quality of life survey-based questionnaire
IM	Intramuscular
IUD	Intrauterine device
kg	Kilogram
KQ	Key Questions
LHRH	Luteinizing Hormone-releasing Hormone
LNG-IUS	Levonorgestrel-releasing intrauterine system
MBL	Menstrual blood loss
mcg	Microgram
MeSH	Medical Subject Heading
mg	Milligram
MIQ	Menorrhagia Impact Questionnaire
mmol	Millimolar
MPA	Medroxyprogesterone acetate
N	Number
NS	Non-significant
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds ratio
PBLAC	Pictorial Blood Loss Assessment Chart
PCOS	Polycystic ovary syndrome
PICOTS	Population, Interventions, Comparators, Outcomes, Timing, Settings
RCT	Randomized Controlled Trials
RR	Relative Risk
SOE	Strength of Evidence
TEP	Technical Expert Panel
TXA	Tranexamic acid

Appendix A. Literature Search Strategies

Table A1: KQ1 search strategy and results from PubMed (pubmed.gov interface)

Terms		Results
#1	uterine hemorrhage[mh:noexp] OR metrorrhagia[mh] OR menstruation disturbances[mh:noexp] OR menorrhagia[mh] OR oligomenorrhea[mh] OR menorrhagia[tiab] OR metrorrhagia[tiab] OR menometrorrhagia[tiab] OR polymenorrhea[tiab] OR oligomenorrhea[tiab] OR hypermenorrhea[tiab] OR dysfunctional uterine bleeding[tiab] OR excessive uterine bleeding[tiab] OR abnormal uterine bleeding[tiab] OR irregular uterine bleeding[tiab] OR ((ovulation dysfunction[tiab] OR ovulatory dysfunction[tiab]) AND (bleeding[tiab] OR hemorrhage[tiab] OR haemorrhage[tiab])) OR ((anovulation[mh] OR anovulation[tiab] OR anovulatory[tiab]) AND (hemorrhage[tiab] OR haemorrhage[tiab] OR bleeding[tiab]))	20,586
#2	therapy[sh:noexp] OR drug therapy[mh] OR drug therapy[sh] OR contraceptives, oral[mh] OR contraceptive agents, female[pa] OR progestins[mh] OR progestins[pa] OR contraceptive devices, female[mh:noexp] OR intrauterine devices[mh] OR anti-inflammatory agents, non-steroidal[mh] OR anti-inflammatory agents, non-steroidal[pa] OR antifibrinolytic agents[mh] OR antifibrinolytic agents[pa] OR complementary therapies[mh] OR cam[sb] OR diet therapy[mh] OR diet therapy[sh] OR exercise therapy[mh] OR psychotherapy[mh]	3,994,137
#3	#1 AND #2 AND english[la] AND humans[mh] AND 1980:2012[dp]	4,846
#4	#3 AND editorial[pt]	30
#5	#3 AND letter[pt]	190
#6	#3 AND comment[pt]	100
#7	#3 AND case reports[pt]	872
#8	#3 AND review[pt]	1,078
#9	#3 AND news[pt]	11
#10	#3 AND newspaper article[pt]	5
#11	#3 AND historical article[pt]	12
#12	#3 AND clinical conference[pt]	7
#13	#3 AND practice guideline[pt]	23
#14	#3 AND meta-analysis[pt]	43
#15	#3 AND congresses[pt]	6
#16	#3 AND consensus development conference[pt]	11
#17	#3 AND retracted publication[pt]	3
#18	#3 AND jsubsetk	21
#19	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	2,090*
#20	#3 NOT #19	2,756
#21	#20 AND (random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR randomized controlled trial[pt] OR controlled clinical trial[pt] OR clinical trial[pt] OR clinical trial[tiab] OR random[tiab] OR randomized[tiab] OR randomised[tiab] OR randomly[tiab] OR assigned[tiab] OR allocated[tiab] OR control[tiab] OR controlled[tiab] OR controls[tiab])	1,374

Key: [dp] publication date; jsubsetk consumer health subset; [la] language; [mh] medical subject heading; [pa] pharmacological action; [pt] publication type; [sb] subset search; [sh] subheading; [tiab] keyword in title or abstract.
* Note: numbers may not tally as some articles are excluded in more than one category.

Table A2: KQ1 search strategy and results from CINAHL (EBSCOhost interface)

Terms		Results
#1	(MH "Uterine Hemorrhage") OR (MH "Metrorrhagia") OR (MH "Menorrhagia") OR (MH "Menstruation Disorders") OR menorrhagia OR metrorrhagia OR menometrorrhagia OR polymenorrhea OR oligomenorrhea OR hypermenorrhea OR dysfunctional uterine bleeding OR excessive uterine bleeding OR abnormal uterine bleeding OR irregular uterine bleeding OR ovulation dysfunction OR ovulatory dysfunction OR ((anovulation OR anovulatory OR cyclic OR cyclical) AND (hemorrhage OR haemorrhage OR bleeding))	1,933
#2	(MH "Therapeutics") OR therapeutic OR therapeutics OR therapy OR therapies OR treatment OR treatments OR management OR (MH "Drug Therapy+") OR drug therapy OR (MH "Contraceptives, Oral+") OR oral contraceptive OR oral contraceptives OR (MH "Intrauterine Devices") OR intrauterine device OR intrauterine devices OR intrauterine system OR intrauterine systems OR IUD OR IUS OR vaginal ring OR (MH "Progestational Hormones+") OR progestin OR progestins OR progestogen OR progestogens OR (MH "Antiinflammatory Agents, Non-Steroidal+") OR non-steroidal anti-inflammatory OR nonsteroidal anti-inflammatory OR non-steroidal antiinflammatory OR nonsteroidal antiinflammatory OR NSAID OR NSAIDs OR (MH "Antifibrinolytic Agents") OR antifibrinolytic OR anti-fibrinolytic OR antifibrinolytics OR anti-fibrinolytics OR tranexamic acid OR aminocaproic acid OR (MH "Natural and Biologically Based Therapies+") OR (MH "Acupuncture+") OR (MH "Alternative Therapies") OR alternative medicine OR complementary medicine OR herbal medicine OR chinese medicine OR acupuncture OR phytotherapy OR (MH "Life Style Changes") OR (MH "Exercise+") OR (MH "Therapeutic Exercise+") OR exercise OR (MH "Weight Loss") OR weight loss OR (MH "Stress Management") OR stress reduction	888,917
#3	#1 AND #2	1,267
#4	#3 AND limiters: English language; Human	376
#5	#3 AND limiters: English language; Human; Exclude MEDLINE records	33

Table A3: KQ1 search strategy and results from EMBASE (OVID interface)

Terms		Results
#1	exp uterus bleeding/ OR menstruation disorder/ OR exp "menorrhagia and metrorrhagia"/ OR (uterine hemorrhage OR metrorrhagia OR menorrhagia OR menometrorrhagia OR polymenorrhea OR oligomenorrhea OR hypermenorrhea OR dysfunctional uterine bleeding OR excessive uterine bleeding OR abnormal uterine bleeding OR irregular uterine bleeding OR ((ovulation dysfunction OR ovulatory dysfunction) AND (bleeding OR hemorrhage OR hemorrhage)) OR ((anovulation OR anovulation OR anovulatory) AND (hemorrhage OR haemorrhage OR bleeding))).mp	27,343
#2	exp oral contraceptive agent/ OR exp intrauterine contraceptive device/ OR exp vagina ring/ OR exp gestagen/ OR exp nonsteroid antiinflammatory agent/ OR exp antifibrinolytic agent/ OR exp alternative medicine/ OR exp traditional medicine/ OR exp acupuncture/ OR exp diet therapy/ OR exp weight reduction/ OR exp stress management/ OR exp relaxation training/	929,093
#3	1 AND 2, limited to human and English language and 1980-2012	6,055
#4	3 AND review.pt	1,823
#5	3 AND conference paper.pt	273
#6	3 AND conference abstract.pt	84
#7	3 AND editorial.pt	96
#8	3 AND letter.pt	213
#9	3 AND note.pt	138
#10	3 AND short survey.pt	148
#11	3 AND case report/	641
#12	3 AND practice guideline/	184
#13	3 AND systematic review/	158
#14	3 AND meta analysis/	138
#15	4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14	3,365*
#16	3 NOT 15	2,690
#17	16 AND (exp clinical trial/ OR exp controlled clinical trial/) AND (exp randomization/ OR randomized controlled trial/ OR (random OR randomly OR randomized OR randomised).mp)	573**

Key: / subject term; exp explode term; .mp keyword, subject term, or substance term; .pt publication type.
* Note: numbers may not tally as some articles are excluded in more than one category.
**After removal of 213 citations duplicated in PubMed, 360 unique citations retained for review

Table A4: KQ2 search strategy and results from PubMed (pubmed.gov interface)

Search terms		Search results
#1	levonorgestrel/ae[mh] OR intrauterine devices, medicated/ae[mh] OR norethindrone/ae[mh] OR ethinyl estradiol/ae[mh] OR medroxyprogesterone acetate/ae[mh] OR mefenamic acid/ae[mh] OR norgestrel/ae[mh] OR genistein/ae[mh] OR dydrogesterone/ae[mh] OR tranexamic acid/ae[mh] OR ethamsylate/ae[mh] OR flurbiprofen/ae[mh] OR naproxen/ae[mh] OR indomethacin/ae[mh] OR metformin/ae[mh] OR progesterone/ae[mh:noexp] OR contraceptives, oral, combined/ae[mh:noexp] OR anti-inflammatory agents, non-steroidal/ae[mh:noexp] OR ((ferric carboxymaltose[supplementary concept] OR ferrous sulfate[supplementary concept] OR exenatide[supplementary concept] OR norgestimate, ethinyl estradiol drug combination[supplementary concept] OR estradiol Valerate, dienogest drug combination[nm] OR dienogest[nm]) AND ae[sh])	23,134
#2	cohort studies[mh] OR product surveillance, postmarketing[mh] OR clinical trial, phase IV[pt] OR databases, factual[mh] OR adverse drug reaction reporting systems[mh] OR case control studies[mh] OR cohort[tiab]	1,373,280
#3	#1 AND #2 AND eng[la] AND humans[mh] AND 1980:2012[dp]	3,142
#4	#3 AND review[pt]	218
#5	#3 AND case reports[pt]	138
#6	#3 AND letter[pt]	124
#7	#3 AND comment[pt]	84
#8	#3 AND meta-analysis[pt]	51
#9	#3 AND practice guideline[pt]	2
#10	#3 AND editorial[pt]	22
#11	#3 AND biography[pt]	1
#12	#3 AND congresses[pt]	2
#13	#3 AND consensus development conference[pt]	2
#14	#3 AND historical article[pt]	2
#15	#3 AND in vitro[pt]	4
#16	#3 AND news[pt]	6
#17	#3 AND retracted publication[pt]	2
#18	#3 NOT (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)	2,611

Key: [tiab] title/abstract word; [mh] MeSH heading; [mh:noexp] MeSH heading not exploded to narrower terms; [la] language; [pt] publication type

Table A5: KQ2 search strategy and results from PubMed (pubmed.gov interface) for update

Search terms		Search results
#1	intrauterine devices, medicated/ae[mh] OR medroxyprogesterone acetate/ae[mh] OR dydrogesterone/ae[mh] OR tranexamic acid/ae[mh] OR ethamsylate/ae[mh] OR metformin/ae[mh] OR progesterone/ae[mh:noexp] OR ((exenatide[supplementary concept] OR cabergoline[supplementary concept) AND ae[sh])	4,055*
#2	cohort studies[mh] OR product surveillance, postmarketing[mh] OR clinical trial, phase IV[pt] OR databases, factual[mh] OR adverse drug reaction reporting systems[mh] OR case control studies[mh] OR cohort[tiab]	1,410,620
#3	#1 AND #2 AND eng[la] AND humans[mh] AND 1980:2012[dp]	672
#4	#3 AND review[pt]	35
#5	#3 AND case reports[pt]	25
#6	#3 AND letter[pt]	26
#7	#3 AND comment[pt]	16
#8	#3 AND meta-analysis[pt]	6
#9	#3 AND practice guideline[pt]	2
#10	#3 AND editorial[pt]	4
#11	#3 AND biography[pt]	0
#12	#3 AND congresses[pt]	0
#13	#3 AND consensus development conference[pt]	0
#14	#3 AND historical article[pt]	2
#15	#3 AND in vitro[pt]	1
#16	#3 AND news[pt]	0
#17	#3 AND retracted publication[pt]	0
#18	#3 NOT (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)	576**

Key: [tiab] title/abstract word; [mh] MeSH heading; [mh:noexp] MeSH heading not exploded to narrower terms; [la] language; [pt] publication type

* Search Strategy for literature update for KQ2 was revised to include on only the interventions identified for KQ1

** Includes 78 new items added with June 2012 update

Appendix B. Abstract Review Form (KQ1)

First Author, Year: _____

Endnote Reference ID #: _____ Abstractor Initials: __ __ __

KQ1A: What is the evidence for the effectiveness of medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) for improving short and long-term outcomes in women with irregular uterine bleeding?

KQ1B: What is the evidence for the effectiveness of medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) for improving short and long-term outcomes in women with abnormal cyclic uterine bleeding?

	Primary Inclusion/Exclusion Criteria			
X-1	1. Paper reports original research (i.e., paper is not a review, editorial, commentary, letter to editor, etc.).	Yes	No	Cannot Determine
X-2	2. Paper published in English language.	Yes	No	Cannot Determine
X-3	3. Eligible study design: randomized controlled trial.	Yes	No	Cannot Determine
	4. Study compares at least two nonsurgical intervention(s) among women with chronic problem bleeding (i.e., abnormal uterine bleeding, menorrhagia, menometrorrhagia, metrorrhagia, uterine hemorrhage, anovulatory bleeding, oligomenorrhea, dysfunctional uterine bleeding).	Yes	No	Cannot Determine
	If "no", check one or more of the following reasons for exclusion:			
X-4	□ Study is basic science, anatomy, imaging, prevalence, physiology, diagnostic, biomarker, or biological mechanism study only.			
X-9	□ Contraceptive efficacy or effectiveness study.			
X-6	□ Study population consists exclusively of women whose bleeding is caused by: structural abnormality (e.g., fibroids, polyps, adenomyosis); cancer; medication side effect; endometrial hyperplasia; or systemic disease (e.g., thyroid disease, coagulopathy).			
X-7	□ Study population consists of post-menopausal women.			
X-8	□ Study evaluates surgical or invasive intervention(s) only or surgical or invasive intervention is the only comparator.			
X-5	□ Other (e.g., intervention unlikely to be used in the primary care setting; intervention not approved for use in the U.S.; bleeding related to pregnancy; acute/emergent bleeding, etc.)			

Retain for:

□ Background/Discussion □ Review of references □ Harms data □ Other_____

COMMENTS:

Appendix C. Abstract Review Form (KQ2)

First Author, Year: _____

Endnote Reference ID #: _____ Abstractor Initials: __ __ __

KQ2. What are the harms, including adverse events, associated with medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) in women with irregular uterine bleeding or abnormal cyclic uterine bleeding?

	Primary Inclusion/Exclusion Criteria			
X-1	1. Paper reports original research (i.e., paper is not a review, editorial, commentary, letter to editor, etc.).	Yes	No	Cannot Determine
X-2	2. Paper reports data from a population* of 1600 or more. **overall population or number of records in the database*	Yes	No	Cannot Determine
X-3	3. An objective of the paper is the reporting of harms data.	Yes	No	Cannot Determine
X-4	4. Paper reports harms data for one or more of the selected interventions addressed in KQ1. (*listed below)* Harms data is associated with one or more selected interventions from KQ1: □ LNG-IUS (Mirena®) □ Progestogen □ Tranexamic acid (Lysteda®) □ Other (i.e., cabergoline, exenatide, ethamsylate, metformin)	Yes	No	Cannot Determine

Retain for:

□ Background/Discussion □ Review of references □ Other_____

COMMENTS:

Appendix D. Full-Text Review Form (KQ1)

First Author, Year: _____

Endnote Reference ID #: _____ Abstractor Initials: __ __ __

KQ1A: What is the evidence for the effectiveness of medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) for improving short and long-term outcomes in women with irregular uterine bleeding?

KQ1B: What is the evidence for the effectiveness of medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) for improving short and long-term outcomes in women with abnormal cyclic uterine bleeding?

	Primary Inclusion/Exclusion Criteria		
X-1	1. Paper reports original research (i.e., paper is not a review, editorial, commentary, letter to editor, etc.)	Yes	No
X-2	2. Eligible study design: randomized controlled trial	Yes	No
	3. Study reports baseline and outcome data for a study population with ≥80 percent women in the target population or reports baseline and outcome data for a subset of women in the target population.	Yes	No
	If "no", classify exclusion as related to one or more of the reasons below:		
X-6	□ Study population >20 percent women whose bleeding is caused by: structural abnormality (e.g., fibroids, polyps, adenomyosis); cancer; medication side effect; endometrial hyperplasia; or systemic disease (e.g., thyroid disease, coagulopathy).		
X-7	□ Study population consists of post-menopausal women.		
X-10	□ Study does not report baseline and outcome data for a study population with ≥80 percent women in the target population or a subset of women in the target population.		
	4. Study informs a key question.	Yes	No
	If "no", classify exclusion as related to one or more of the reasons below:		
X-4	□ Study is basic science, anatomy, imaging, prevalence, physiology, diagnostic, biomarker, or biological mechanism study only		
X-9	□ Study evaluates contraceptive efficacy or effectiveness only		
X-8	□ Study evaluates surgical or invasive intervention(s) only or surgical or invasive intervention is the only comparator		
X-5	□ Other (e.g., intervention unlikely to be used in the primary care setting; intervention not approved for use in the U.S.; bleeding related to pregnancy; acute/emergent bleeding, etc.).		
	If "yes", check one or both KQs below:		
	□ KQ1A: Effectiveness of a medical, behavioral or complementary and alternative medicine (CAM) intervention (e.g. hormonal treatment, weight loss, or acupuncture) for improving short and long-term outcomes in women with irregular abnormal bleeding		
	□ KQ1B: Effectiveness of a medical, behavioral or complementary and alternative medicine (CAM) intervention (e.g. hormonal treatment, weight loss, or acupuncture) for improving short and long-term outcomes in women with abnormal cyclic bleeding		
	□ Unclear/ discuss		

Retain for:

□ Background/Discussion □ Review of references □ Harms data □ Other_____

COMMENTS:

Appendix E. Full-Text Review Form (KQ2)

First Author, Year: _____

Endnote Reference ID #: _____ Abstractor Initials: __ __ __

KQ2. What are the harms, including adverse events, associated with medical, behavioral, and complementary and alternative medicine interventions (e.g., hormonal treatment, weight loss, or acupuncture) in women with irregular uterine bleeding or abnormal cyclic uterine bleeding?

	Primary Inclusion/Exclusion Criteria		
X-1	1. Paper reports original research (i.e., paper is not a review, editorial, commentary, letter to editor, etc.).	Yes	No
X-2	2. Paper reports data from a population of 1600 or more. **overall population or number of records in the database*	Yes	No
X-4	3. Paper reports harms from one or more of the selected interventions included in KQ1. *If "yes", specify below*. □ LNG-IUS (Mirena®) □ Progestogen including: • depot or oral medroxyprogesterone • norethisterone/ norethindrone • oral dydrogesterone • vaginal progesterone • progesterone coil □ Tranexamic acid (Lysteda®) □ Other including: • cabergoline • ethamsylate • exenatide • metformin	Yes	No
	4. Study addresses KQ2. *If "no", classify exclusion as related to one or more of the reasons below.*	Yes	No
X-3	□ Reporting of harms is from a general population or reporting of harms is not an objective of the paper/study.		
X-5	□ Study is basic science, anatomy, imaging, prevalence, physiology, diagnostic, biomarker, or biological mechanism study only.		
X-6	□ Study of men only.		
X-7	□ Study population consists of post-menopausal women or a population aged over 65 years.		
X-8	□ Other		

Retain for:

□ Background/Discussion □ Review of references □ Other_____

COMMENTS:

Appendix F. Cochrane Risk of Bias Tool

Use the modified Cochrane Collaboration tool to assess risk of bias for randomized controlled trials. Bias is assessed as a judgment (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other).

AUB KQ1 Risk of Bias Assessment (Reference ID #)

Domain	Description	High Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Reviewer Assessment	Reviewer Comments
Selection bias ***Random sequence generation***	Described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence	Random sequence generation method should produce comparable groups	Not described in sufficient detail	**High** **Low** **Unclear**	
Selection bias ***Allocation concealment***	Described the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrollment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	Intervention allocations likely could not have been foreseen in before or during enrollment	Not described in sufficient detail	**High** **Low** **Unclear**	
Reporting bias ***Selective reporting***	Stated how the possibility of selective outcome reporting was examined by the authors and what was found	Reporting bias due to selective outcome reporting	Selective outcome reporting bias not detected	Insufficient information to permit judgment†	**High** **Low** **Unclear**	
Other bias ***Other sources of bias***	Any important concerns about bias not addressed above*	Bias due to problems not covered elsewhere in the table	No other bias detected	There may be a risk of bias, but there is either insufficient information to assess whether an important risk of bias exists or insufficient rationale or evidence that an identified problem will introduce bias	**High** **Low** **Unclear**	

* If particular questions/entries were pre-specified in the study's protocol, responses should be provided for each question/entry.
† It is likely that the majority of studies will fall into this category.
Assess each main or class of outcomes for each of the following. Indicate the specific outcome.

AUB KQ1 Risk of Bias Assessment (Reference ID #)

Outcome:

Domain	Description	High Risk of Bias	Low Risk of Bias	Unclear Risk of Bias	Reviewer Assessment	Reviewer Comments
Performance bias ***Blinding (participants and personnel)***	Described all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	Blinding was likely effective.	Not described in sufficient detail	**High** **Low** **Unclear**	
Detection bias ***Blinding (outcome assessment)***	Described all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provided any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.	Blinding was likely effective.	Not described in sufficient detail	**High** **Low** **Unclear**	
Attrition bias ***Incomplete outcome data***	Described the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. Stated whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported.	Attrition bias due to amount, nature or handling of incomplete outcome data.	Handling of incomplete outcome data was complete and unlikely to have produced bias	Insufficient reporting of attrition/exclusions to permit judgment (e.g., number randomized not stated, no reasons for missing data provided)	**High** **Low** **Unclear**	

Appendix G. Cochrane Risk of Bias Criteria

Criteria for judging risk of bias using the Cochrane Collaboration Risk of Bias Tool[a]

Bias	Judgment	Criteria
RANDOM SEQUENCE GENERATION Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.	'Low risk' of bias.	The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization*. *Minimization may be implemented without a random element, and this is considered to be equivalent to being random.
	'High risk' of bias.	The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: • Allocation by judgement of the clinician; • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention.
	'Unclear risk' of bias.	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.
ALLOCATION CONCEALMENT Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.	'Low risk' of bias.	Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • Central allocation (including telephone, web-based and pharmacy-controlled randomization); • Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, sealed envelopes.
	'High risk' of bias.	Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • Using an open random allocation schedule (e.g. a list of random numbers); • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); • Alternation or rotation; • Date of birth; • Case record number; • Any other explicitly unconcealed procedure.
	'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.
SELECTIVE REPORTING Reporting bias due to selective outcome reporting.	'Low risk' of bias.	Any of the following: • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Bias	Judgment	Criteria
	'High risk' of bias.	Any one of the following: • Not all of the study's pre-specified primary outcomes have been reported; • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • The study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	'Unclear risk' of bias.	Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.
OTHER BIAS Bias due to problems not covered elsewhere in the table.	'Low risk' of bias.	The study appears to be free of other sources of bias.
	'High risk' of bias.	There is at least one important risk of bias. For example, the study: • Had a potential source of bias related to the specific study design used; or • Has been claimed to have been fraudulent; or • Had some other problem.
	'Unclear risk' of bias.	There may be a risk of bias, but there is either: • Insufficient information to assess whether an important risk of bias exists; or • Insufficient rationale or evidence that an identified problem will introduce bias.
BLINDING OF PARTICIPANTS AND PERSONNEL Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.	'Low risk' of bias.	Any one of the following: • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	'High risk' of bias.	Any one of the following: • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgment of 'Low risk' or 'High risk'; • The study did not address this outcome.
BLINDING OF OUTCOME ASSESSMENT Detection bias due to knowledge of the allocated interventions by outcome assessors.	'Low risk' of bias.	Any one of the following: • No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; • Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	'High risk' of bias.	Any one of the following: • No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; • Blinding of outcome assessment, but likely that the blinding could have been broken and the outcome measurement is likely to be influenced by lack of blinding.
	'Unclear risk' of bias.	Any one of the following: • Insufficient information to permit judgment of 'Low risk' or 'High risk'; • The study did not address this outcome.

Bias	Judgment	Criteria
INCOMPLETE OUTCOME DATA Attrition bias due to amount, nature or handling of incomplete outcome data.	'Low risk' of bias.	Any one of the following: • No missing outcome data; • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; • Missing data have been imputed using appropriate methods.
	'High risk' of bias.	Any one of the following: • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; • Potentially inappropriate application of simple imputation.
	'Unclear risk' of bias.	Any one of the following: • Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided); • The study did not address this outcome.

Note: [a] Adapted from the Cochrane Collaboration Risk of Bias Tool. See Higgins JP, Altman DG, Sterne JA. Chapter 8: Assessing the risk of bias in included studies. In: Higgins JP, Green S, eds. Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration; 2011.

Appendix H. Thresholds for Quality Assessment

Quality assessment thresholds for *Cochrane Risk of Bias (RoB) Tool***:** There are three categories for describing the quality of studies: "Good", "Fair", and "Poor". In order to assign a study to a category, we need to establish the threshold between good and fair quality studies and between fair and poor quality studies. Cochrane Collaboration uses strict criteria for the quality ratings.

Cochrane Collaboration criteria for quality ratings:

- *A good quality study must meet all criteria (Low RoB).*
- *A fair quality study does not meet, or it is not clear that it meets, at least one criterion, but it has no known important limitation that could invalidate its results (Moderate RoB).*
- *A poor quality study has important limitations and/or at least one criterion is not met (High RoB).*

Modifications of criteria for quality ratings:

- *If all criteria are rated as "low" = Low RoB =* ***Good Quality***
- *If one criterion is rated as "high" or 1-2 criteria are "unclear", and the assessment is that this was* ***unlikely*** *to have biased the outcome, and there is no known important limitation that could invalidate the results = Low RoB =* ***Good Quality***
    - *Example: not blinded, but blinding was not possible and based upon design and outcomes, it is unlikely that the lack of blinding could have affected the outcome measure or other factor that would introduce bias*
- *If one criterion is rated as "high" or 1-2 criteria are "unclear", and the assessment is that this was* ***likely*** *to have biased the outcome, and there is no known important limitation that could invalidate the results = Moderate RoB =* ***Fair Quality***
    - *Could be* ***poor****, if the factors were considered to combine to important limitations*
- *If one criterion is rated as "high" and 3 are "unclear = Moderate RoB =* ***Fair Quality***
    - *Could be* ***poor****, if the factors were considered to combine to important limitations*
- *If two criteria are rated as "high", and all other criteria are 'low', and the assessment that this was* ***unlikely*** *to have biased the outcome, and there are no known important limitations that could invalidate the results = Moderate RoB =* ***Fair Quality***
- *If two criteria are rated as "high", and all other criteria are 'low', and the assessment that this was* ***likely*** *to have biased the outcome, and there are important limitations that could invalidate the results = High RoB =* ***Poor Quality***
- *If three or more criteria are rated as "high" = High RoB =* ***Poor Quality***
- *If four or more criteria are rated as "unclear"= High RoB =* ***Poor Quality***

Low RoB criteria	High RoB criteria	Unclear RoB criteria	Rating
7	0	0	Good
5-6	0-1	0-2	Good or Fair
3-5	0-2	0-3	Fair or Poor
0-4	2-7	0-7	Poor
0-3	0-7	4-7	Poor

Appendix I. Risk of Bias and Quality Score for Individual Studies

Author, Year	Random Sequence Generation	Allocation Concealment	Selective Reporting	Blinding (patients and personnel)	Blinding (outcome assessment)	Incomplete Outcome Data	Other Bias	Quality Score
Abu Hashim et al., 2012[1]	+	+	+	-	-	+	+	Fair
Andersch et al., 1988[2]	?	?	?	?	?	+	+	Poor
Bonnar and Sheppard, 1996[3]	+	?	?	-	-	+	+	Poor
Cai and Wu, 2009[4]	+	+	+	?	?	+	+	Fair
Cameron et al., 1987[5]	?	?	?	-	-	?	?	Poor
Cameron et al., 1990[6]	?	?	+	?	?	+	+	Poor
Davis et al., 2000[7]	+	+	+	+	+	+	+	Good
Elkind-Hirsch et al., 2008[8]	+	?	+	-	-	-	+	Poor
Endrikat et al., 2009[9]	+	-	+	-	?	+	-	Poor
Fleming et al., 2002[10]	+	+	+	+	+	-	+	Fair
Fraser and McCarron, 1991[11]	?	?	+	-	-	-	+	Poor
Fraser et al., 1981[12]; 1984[13]	?	?	+	+	+	+	+	Fair
Fraser et al., 2011[14]	+	+	?	+	+	+	+	Good
Freeman et al., 2011[15]	?	?	+	+	?	+	+	Fair
Grover et al., 1990[16]	?	?	?	?	?	?	-	Poor
Hall et al., 1987[17]	+	+	+	+	+	-	+	Fair
Irvine et al., 1998[18]	+	+	?	?	-	+	+	Fair
Jedel et al., 2011[19]	+	+	+	-	?	-	+	Poor
Jensen et al., 2011[20]	+	+	?	+	+	+	+	Good
Karakus et al., 2009[21]	+	-	?	-	?	-	?	Poor
Kaunitz et al., 2010[22]	+	+	+	-	?	+	+	Fair
Kennedy et al., 2002[23]	+	+	+	-	-	-	+	Poor
Kriplani et al., 2006[24]	+	?	?	-	-	-	+	Poor
Kucuk and Ertan, 2008[25]	-	-	?	?	?	+	+	Poor
Lahteenmaki et al., 1998[26]	+	+	?	?	-	+	+	Poor
Lukes et al., 2010[27]	+	+	+	+	+	+	+	Good
Moghetti et al., 2000[28]	?	?	?	+	+	?	+	Poor

Author, Year	Random Sequence Generation	Allocation Concealment	Selective Reporting	Blinding (patients and personnel)	Blinding (outcome assessment)	Incomplete Outcome Data	Other Bias	Quality Score
Najam et al., 2010[29]	+	?	?	-	-	+	+	Poor
Oner and Muderris, 2011[30]	?	?	+	?	?	-	?	Poor
Ornstein et al., 2011[31]	?	?	+	-	?	-	-	Poor
Paoletti et al., 1996[32]	+	?	+	+	+	+	+	Good
Preston et al., 1995[33]	+	+	?	+	+	-	+	Fair
Protheroe et al., 2007[34]	+	+	?	-	-	+	?	Poor
Reid and Vitaren-Kari, 2005[35]	+	+	?	-	-	+	+	Poor
Shabaan etal., 2011[36]	+	-	+	-	?	+	-	Poor
Tsang et al., 1987[37]	?	?	+	+	+	-	+	Poor
van Eijkeren et al., 1992[38]	+	+	+	+	+	-	+	Fair
Vargyas et al., 1987[39]	+	+	+	+	+	+	+	Good
Vuorma et al., 2004[40, 41]	+	+	+	-	-	+	+	Poor
Totals								
	+	27	19	23	14	13	24	31	
	?	11	16	16	8	13	3	4	
	-	1	4	0	17	13	12	4	

Notes: Low risk of bias: +; High risk of bias: -; Unclear risk of bias: ?

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Appendix J. Evidence Table

AUB KQ1 Evidence Table (Reference ID #121)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Cai and Wu, 2009 **Country:** China **Enrollment period:** November 2004 to October 2005 **Intervention setting:** Outpatient **Funding:** NR **Author industry relationship disclosures:** NR **Study Design:** RCT **Blinding:** Patients	**Intervention:** Mind tranquilizing and menstruation promoting method. Acupoints: Shenting (GV24), bilateral Siguan and bilateral Sanyinjiao (SP6). Shenting was transversely punctured and Siguan and Sanyinjiao were needled perpendicularly. **Comparator:** Routine acupuncture method for treating delayed menstrual cycle of the liver-*qi* stagnation type. Acupoints: bilateral Xingjian (LR2), Ligou (LR 5), Xuehai (Sp 10), Diji (SP8) and Zigong (EX-CA1) all perpendicularly punctured. Both groups used No. 32 filiform needles manipulated with the even method. After arrival of *qi* needles retained for 30 minutes and manipulated every 10 minutes. Treatment given every other day, with 2 day interval in the weekend for 3 menstrual cycles.	**Inclusion criteria:** • Delayed menstrual cycle (TCM diagnosis of dysfunctional uterine bleeding of the ovulatory type) with menstrual cycles lasting 36 to 50 days **Exclusion criteria:** Organic pathologic changes **N at enrollment:** **G1:** 23 **G2:** 17 **N at followup:** **G1:** 21 **G2:** 16 **Age, range in years:** **G1+G2:** (18, 42) **BMI:** NR **Parity:** NR **Race/ethnicity:** NR	NR	Therapeutic effect on disease condition, n (%): Cured[a]: **G1:** 16 (76.19) **G2:** 1 (6.25) Markedly relieved[b]: **G1:** 3 (14.29) **G2:** 5 (31.25) Improved[c]: **G1:** 2 (9.52) **G2:** 9 (56.25) Failed[d]: **G1:** 0 (0) **G2:** 1 (6.25) **G1 vs. G2:** p<0.05 Therapeutic effects for regulating menstruation, n (%): Cured: **G1:** 14 (66.67) **G2:** 3 (18.75) Markedly relieved: **G1:** 4 (19.05) **G2:** 4 (25.00) Improved: **G1:** 3 (14.29) **G2:** 6 (37.50) Failed: **G1:** 0 (0) **G2:** 3 (18.75) **G1 vs. G2:** p<0.05 Therapeutic effects on symptoms, n (%): Cured:	**Overall quality:** Fair **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Low Blinding patients/personnel: Unclear Blinding outcome assessment: Unclear Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
	Groups: **G1:** Mind tranquilizing and menstruation promoting acupuncture **G2:** Routine acupuncture **Followup:** 3 cycles			**G1:** 11 (52.38) **G2:** 2 (12.5) Markedly relieved: **G1:** 9 (42.86) **G2:** 5 (31.25) Improved: **G1:** 1 (4.76) **G2:** 8 (50.0) Failed: **G1:** 0 (0) **G2:** 1 (6.25) **G1 vs. G2:** p<0.05 **Bleeding:** NR **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** **G1:** 4/5 **G2:** 1/1 **Time to conception:** NR **Additional interventions:** NR	

Table Notes: [a] Disappearance of all symptoms and integral score decreased by ≥90%; [b] Disappearance of most of the symptoms, and the integral score decreased by ≥70%, but <90%; [c] Improved: Alleviation of the symptoms and the integral score decreased by ≥30%, but <79%; [d] No obvious improvement in the symptoms and the integral score decreased by <30%.

AUB KQ1 Evidence Table (Reference ID #631)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Davis et al., 2000 **Country:** United States **Enrollment period:** May 1997 to October 1998 **Intervention setting:** 16 sites **Funding:** Ortho-McNeil Pharmaceutical Corporation **Author industry relationship disclosures:** 5/5 **Study Design:** RCT **Blinding:** Patients, investigators	**Intervention:** Days 1-7: 0.180 mg norgestimate/0.035 mg ethinyl estradiol; Days 8-14: 0.215 mg norgestimate/0.035 mg ethinyl estradiol; Days 15-21: 0.250 mg norgestimate/0.035 mg ethinyl estradiol; Days 22-28: inactive tablets **Comparator:** Days 1-28: placebo tablets **Groups:** **G1:** Triphasic norgestimate/ethinyl estradiol **G2:** Placebo **Followup:** 3 28-day treatment cycles (84 days)	**Inclusion criteria:** • Aged 15 to 50 years Good general health Not pregnant or nursing At least 2-month history of menorrhagic, menometrorrhagic, oligomenorrheic or polymenorrheic dysfunctional uterine bleeding not attributed to systemic disease or structural pathology **Exclusion criteria:** History of endometrial ablation and undergone dilation and curettage within 90 days before screening visit **N at enrollment:** **G1:** 101 **G2:** 100 (ITT) **G1:** 97 **G2:** 95 **N at followup:** **G1:** 60 **G2:** 64 **Age, mean years ± SD:** **G1:** 29.8 ± 8.9 **G2:** 29.3 ± 8.1 **BMI:** NR	**Bleeding:** Duration of abnormal uterine bleeding, mean months ± SD: **G1:** 77.4 ± 73.5 **G2:** 68.3 ± 71.2 Duration of abnormal uterine bleeding, median months: **G1:** 67.6 **G2:** 40.5 Bleeding pattern history,[a] n (%): Metrorrhagia: **G1:** 23 (23.7) **G2:** 26 (27.4) Menometrorrhagia: **G1:** 29 (29.9) **G2:** 33 (34.7) Oligomenorrhea: **G1:** 54 (55.7) **G2:** 54 (56.8) Polymenorrhea: **G1:** 20 (20.6) **G2:** 20 (21.1) Hemoglobin, mean g/dl ± SD: **G1:** 12.7 ± 1.2 **G2:** 12.85 ± 1.1 **Quality of life:** SF-36 score,[b] mean:[c] Physical functioning: **G1:** 88.60 **G2:** 88.71 Role functioning/physical:	Investigator-rated overall assessment of symptom resolution, %: Excellent: **G1:** 41.2 **G2:** 10.5 Good: **G1:** 26.8 **G2:** 15.8 Fair: **G1:** 13.4 **G2:** 9.5 No change: **G1:** 10.3 **G2:** 46.3 Worse: **G1:** 2.1 **G2:** 2.1 Unable to evaluate: **G1:** 6.2 **G2:** 15.8 **G1 vs. G2:** p<0.001 Subject-rated assessment of symptom improvement, %: Much improved: **G1:** 49.5 **G2:** 19.8 Improved: **G1:** 23.7 **G2:** 19.8 Slightly improved: **G1:** 14.0 **G2:** 5.8 No change: **G1:** 8.6 **G2:** 47.7 Worse:	**Overall quality:** Good **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Low Blinding patients/personnel: Low Blinding outcome assessment: Low Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		Weight, mean pounds ± SD: **G1:** 173.4 ± 55.9 **G2:** 171.1 ± 48.5 **Race, n (%):** White: **G1:** 73 (75.3) **G2:** 66 (69.5) Black: **G1:** 16 (16.5) **G2:** 22 (23.2) Asian: **G1:** 4 (4.1) **G2:** 1 (1.1) Other: **G1:** 4 (4.1) **G2:** 6 (6.3)	**G1:** 87.10 **G2:** 89.12 Bodily pain: **G1:** 70.99 **G2:** 74.81 General health: **G1:** 75.00 **G2:** 77.36 Vitality: **G1:** 57.04 **G2:** 60.06 Social functioning: **G1:** 84.01 **G2:** 85.15 Role functioning/ emotional: **G1:** 78.85 **G2:** 82.75 Mental health: **G1:** 72.52 **G2:** 75.29 Reported health transition: **G1:** 41.13 **G2:** 43.24 Sexual functioning: **G1:** 19.27 **G2:** 17.35	**G1:** 2.2 **G2:** 3.5 Don't know: **G1:** 2.2 **G2:** 3.5 **G1 vs. G2:** p<0.001 **Quality of life:** SF-36[b] score,[c] mean change from baseline ± SD:[d] Physical functioning: **G1:** 4.19 ± 16.83 **G2:** 0.47 ± 13.35 **G1 vs. G2:** p<0.001 Role functioning/physical: **G1:** 1.61 ± 24.59 **G2:** 1.18 ± 30.11 **G1 vs. G2:** p=0.160 Bodily pain: **G1:** 4.45 ± 22.58 **G2:** 0.15 ± 20.77 **G1 vs. G2:** p=0.896 General health: **G1:** 1.58 ± 15.02 **G2:** 1.12 ± 11.29 **G1 vs. G2:** p=0.265 Vitality: **G1:** 6.18 ± 17.70 **G2:** 3.94 ± 17.22 **G1 vs. G2:** p=0.410 Social functioning: **G1:** 0.40 ± 20.06 **G2:** -1.76 ± 21.58 **G1 vs. G2:** p=0.735 Role functioning/emotional: **G1:** 6.09 ± 30.67 **G2:** 2.75 ± 29.64 **G1 vs. G2:** p=0.694 Mental health: **G1:** 4.52 ± 14.03	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				G2: 1.65 ± 17.12 **G1 vs. G2:** p=0.935 Reported health transition: **G1:** -4.03 ± 28.62 **G2:** -4.41 ± 21.88 **G1 vs. G2:** p=0.109 Sexual functioning: **G1:** -2.51 ± 22.75 **G2:** -0.10 ± 26.05 **G1 vs. G2:** p=0.404 **Patient satisfaction:** **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR **Adverse events:** Discontinued study prematurely, n (%): **G1:** 16 (15.8) **G2:** 19 (19) Discontinued due to adverse events, n: **G1:** 4 **G2:** 3	

Table Notes: Blood loss estimated from PBLAC Higham et al.; [a] Subjects could have more than one category of bleeding pattern history; [b] Medical Outcome Study, 36-item short-form health survey plus five items from the full set on sexual functioning; [c] Quality of life scores transformed to a 0-100 scale with a higher score indicating better quality of life, except for reported health transition and sexual functioning, for which a higher score indicates a lower quality; [d] Significance is computed using analysis of covariance with adjustment for baseline score, study centers, and interaction terms.

AUB KQ1 Evidence Table (Reference ID #1431)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)[a]	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Elkind-Hirsch et al., 2008 **Country:** United States **Enrollment period:** August 2006 to June 2007 **Intervention setting:** Outpatient clinics **Funding:** Amylin Pharmaceuticals, Inc/Eli Lilly Corp **Author industry relationship disclosures:** 2/5 **Study Design:** RCT **Blinding:** None	**Intervention:** Exenatide 5 µg by subcutaneous injection twice a day and increased to 10 µg twice per day after 1 month. **Comparator:** Metformin 500 mg for two weeks and gradually increased to 1000 mg twice a day; Combination: metformin 500 mg for two weeks and gradually increased to 1000 mg twice a day plus exenatide 5 µg by subcutaneous injection twice a day and increased to 10 µg twice per day after 1 month. All groups received treatment for 24 weeks. **Groups:** **G1:** Exenatide **G2:** Metformin **G3:** Combination metformin and exenatide **Followup:** 24 weeks	**Inclusion criteria:** Aged 18 to 40 years Polycystic ovary syndrome Overweight/obese (BMI >27) Menstrual disorders (fewer than six menstruations in 12 months) One of the following two criteria: either clinical and/or biochemical hyperandrogenism (excluding secondary causes) and/or polycystic ovaries **Exclusion criteria:** Diabetics Smokers Those who used injectable hormonal contraceptive within 6 months Those taking sex hormones, drugs that affect gastrointestinal motility or carbohydrate metabolism, or lipid-lowering and/or anti-obesity drugs within 3 months of the study **N at enrollment:** **G1:** 20 **G2:** 20 **G3:** 20 **N at followup:** **G1:** 14	**Bleeding:** Cycle changes measured by menstrual frequency index,[b] mean ± SD: **G1:** 0.22 ± 0.04 **G2:** 0.21 ± 0.04 **G3**: 0.29 ± 0.04 Absolute weight, mean kg ± SD: **G1:** 110.5 ± 6 **G2:** 113.4 ± 7 **G3:** 112 ± 8 Abdominal girth, mean cm ± SD: **G1:** 120.4 ± 4.5 **G2:** 123.4 ± 4.3 **G3:** 122 ± 4.4 BMI, mean kg/m^2 ± SD: **G1:** 40.3 ± 2 **G2:** 43.3 ± 2 **G3:** 40.9 ± 2	**Bleeding:** Cycle changes measured by menstrual frequency index,[b] mean ± SD: **G1:** 0.57 ± 0.08 **G2:** 0.49 ± 0.08 **G3:** 0.83 ± 0.08 **G1+G2+G3 vs. BL:** p=0.0001 **G3 vs. G1:** p=0.091 **G3 vs. G2:** p=0.018 Ovulatory rate,%: **G1:** 50 **G2:** 29 **G3:** 86 **G3 vs. G1:** p<0.001 **G3 vs. G2**: p<0.001 **Weight changes:** Weight loss, mean kg ± SD: **G1:** 3.2 ± 0.1 **G2:** 1.6 ± 0.2 **G3:** 6 ± 0.5 **G1+G2+G3 vs. BL:** p=0.001 **G1 vs. G2:** p=0.019 **G3 vs. G2:** p=0.003 Abdominal girth, mean ± SD: **G1:** 119.6 ± 4.3 **G2:** 123.9 ± 4.4 **G3:** 116 ± 4.3 **G1+G2+G3 vs. BL:** p=0.047 **G3 vs. G2:** p=0.04	**Overall quality:** Poor **Risk of bias:** Randomization: Low Allocation concealment: Unclear Selective reporting: Low Blinding patients/personnel: High Blinding outcome assessment: High Incomplete outcome reporting: High Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)[a]	Outcome Measure(s)	Overall Quality Risk of Bias
		G2: 14 **G3:** 14 **Age, mean years ± SD:** **G1:** 28.2 ± 1.1 **G2:** 27.7 ± 1.3 **G3:** 32.1 ± 0.7 **G1 vs. G2 vs. G3:** p=NS **BMI, mean kg/m^2 ± SD:** **G1:** 39.9 ± 1.5 **G2:** 41.3 ± 1.8 **G3:** 41.2 ± 1.7 **G1 vs. G2 vs. G3:** p=NS **Parity:** NR **Race, n (%):** Caucasian: **G1+G2+G3:** 40 (67) African-American: **G1+G2+G3:** 20 (33)		BMI, mean kg/m^2 ± SD: **G1:** 39.3 ± 2 **G2:** 42.3 ± 2 **G3:** 39.2 ± 2 **G1+G2+G3 vs. BL:** p<0.0001 **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR **Adverse events, n (%):** Nausea: **G1:** 3 (15) **G2:** 4 (20) **G3:** 9 (45) Diarrhea: **G1:** 0 **G2:** 6 (30) **G3:** 2 (20) Bloating: **G1:** 0 **G2:** 2 (10)	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)[a]	Outcome Measure(s)	Overall Quality Risk of Bias
				G3: 1 (5) Vomiting: **G1:** 1 (5) **G2:** 1 (5) **G3:** 2 (10) Cramping (gastrointestinal): **G1:** 1 (5) **G2:** 0 **G3:** 0 Headache: **G1:** 1 (5) **G2:** 0 **G3:** 0 Indigestion/heartburn: **G1:** 0 **G2:** 0 **G3:** 2 (10) Stomachache: **G1:** 0 **G2:** 1 (5) **G3:** 0 Constipation: **G1:** 0 **G2:** 1 (5) **G3:** 1 (5) Fatigue: **G1:** 0 **G2:** 2 (10) **G3:** 1 (5) Dizzy: **G1:** 0 **G2:** 0 **G3:** 2 (10) Injection site pain/bruise: **G1:** 1 (5) **G2:** NA **G3:** 2 (10) Pregnancy: **G1:** 1 (5) **G2:** 2 (10)	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)[a]	Outcome Measure(s)	Overall Quality Risk of Bias
				G3: 1 (5) Menstrual cramps: **G1:** 0 **G2:** 1 (5) **G3:** 0 Dysfunctional menstrual bleeding: **G1:** 1 (5) **G2:** 1 (5) **G3:** 0 Acne: **G1:** 0 **G2:** 0 **G3:** 1 (5) Migraines: **G1:** 0 **G2:** 1 (5) **G3:** 0 Hot flashes: **G1:** 0 **G2:** 1 (5) **G3:** 0	

Table Notes: [a] Baseline measures for the subset of subjects who competed the trial (n=14 in each group); [b] Cycle event rate (normalized to 12 per 52 weeks)

AUB KQ1 Evidence Table (Reference ID #564)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Fleming et al., 2002 **Country:** United Kingdom **Enrollment period:** NR **Intervention setting:** NR **Funding:** Sponsored by the Scottish Office **Author industry relationship disclosures:** NR **Study Design:** RCT **Blinding:** Patients, investigators	**Intervention:** Metformin 850 mg once per day for first week, then 850 mg twice daily for 15 more weeks **Comparator:** Placebo **Groups:** **G1:** Metformin **G2:** Placebo **Followup:** 16 weeks	**Inclusion criteria:** • Aged <35 years • Oligomenorrhea (cycle length ≥41 days; <8 cycles per year) or amenorrhea and PCOS **Exclusion criteria:** Significant hyperprolactinemia Abnormal thyroid function tests Congenital adrenal hyperplasia **N at enrollment:** **G1:** 45 **G2:** 47 **N at followup:** **G1:** 26 **G2:** 39 **Age, mean years (95% CI):** **G1:** 28.6 (26.9 to 30.3) **G2:** 29.2 (27.5 to 30.7) **BMI, mean kg/m^2:** **G1:** 34.2 **G2:** 35.0	**Menstrual cycle:** Menses per year, mean (95% CI): **G1:** 4.6 (3.5, 5.6) **G2:** 4.0 (3.1, 4.9) **Reproductive hormones:** Day 1 estradiol, mean pmol/liter (95% CI): **G1:** 142 (123, 161) **G2:** 164 (110, 217) Day 1 testosterone, mean nmol/l (95% CI): **G1:** 3.1 (2.4, 3.8) **G2:** 3.8 (3.4, 4.5)	**Menstrual cycle:** Observation weeks, n: **G1:** 345 **G2:** 503 Luteal weeks, n (luteal ratio %): **G1:** 78 (23) **G2:** 66 (13) **G1 vs. G2:** p<0.001 Luteal phase with Pmax <7 ng/ml, n (%): **G1:** 2 (8) **G2:** 5 (13) **G1 vs. G2:** p=NS Time to first ovulation, mean days (95% CI): **G1:** 23.6 (17, 30) **G2:** 41.8 (28, 56) **G1 vs. G2:** p=0.02 **Reproductive hormones:** Day 8 estradiol, mean pmol/l (95% CI): **G1:** 226 (150, 302) **G2:** 183 (127, 240) **G1 vs. BL:** p<0.03 **G2 vs. BL:** p=NS Day 8 testosterone, mean nmol/l (95% CI): **G1:** 3.5 (2.8, 4.2) **G2:** 4.2 (3.5, 4.9) **G1 vs. BL:** p=NS **G2 vs. BL:** p=NS **Metabolic parameters:**	**Overall quality:** Fair **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Low Blinding patients/personnel: Low Blinding outcome assessment: Low Incomplete outcome reporting: High Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				BMI at week 14, mean kg/m^2: **G1:** 34.6 **G2:** 35.6 **G1 vs. BL:** p=0.03 **G2 vs. BL:** p=0.04 **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** Pregnancies during study: **G1:** 5 **G2:** 3 Pregnancies in patients who declared wish to conceive: **G1:** 4/23 **G2:** 1/19 **G1 vs. G2:** p=0.23 **Additional interventions:** NR	

AUB KQ1 Evidence Table (Reference ID #25)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Jedel et al., 2011 **Country:** Sweden **Enrollment period:** November 2005 to January 2008 **Intervention setting:** Sahlgrenska University Hospital **Funding:** Grants from the Osher center for Integrative medicine, Swedish Medical Research Council, Novo Nordisk Foundation, Wilhelm and Martina Lundgren's Science fund, Haljmar Svensson Foundation, Tore Nilson Foundation, Ake Wiberg Foundation, Alderbert Research Foundation, Ekhaga Foundation and the Swedish Federal Government **Author industry relationship disclosures:** None **Study Design:**	**Intervention(s):** Low frequency electro-acupuncture[a]: Western medical acupuncture given twice weekly for 2 weeks, once a week for 6 weeks and once every other week for 8 weeks (total 14 treatments over 16 weeks) **Comparator(s):** Physical exercise: 16 weeks of regular exercise including brisk walking, cycling, or any other aerobic exercise at pace faster than normal walking that could be sustained for at least 30 min at least 3 days per week. No active intervention. **Groups:**[b] **G1:** Acupuncture **G2:** Exercise **G3:** No intervention **Followup:** 12 week observation followed by 16 weeks of intervention followed by 16 weeks followup (44 week study)	**Inclusion criteria:** • Ultrasound verified polycystic ovaries with ≥12 follicles 2 to 9 mm and/or ovarian volume ≥10 ml in one or both ovaries together with either oligomenorrhea, amenorrhea, and/or clinical signs of hyperandrogenism (hirsutism or acne) **Exclusion criteria:** Aged ≥38 years Any pharmacological treatment within 12 weeks or breast feeding within 24 weeks of study entry Cardiovascular disease, diabetes mellitus, or endocrine or neoplastic causes of hyperandrogenemia including androgen secreting tumors, Cushing's syndrome, congenital adrenal hyperplasia and hyperprolactinemia **N at enrollment:** **G1:** 33 **G2:** 34 **G3:** 17 **N at followup:** 12 week observation period:	**Bleeding:** Menstrual frequency, mean days per month ± SD: **G1:** 0.28 ± 0.28 **G2:** 0.26 ± 0.33 **G3:** 0.23 ± 0.28	**Bleeding:** Change in menstrual frequency at week 16 from baseline, mean days per month ± SD (% change): **G1:** 0.41 ± 0.33 (146) **G2:** 0.14 ± 0.33 (58) **G3:** -0.04 ± 0.007 (-17) **G1 vs. BL:** p<0.001 **G2 vs. BL:** p=NS **G3 vs. BL:** p=NS Change in menstrual frequency at week 32 from baseline, mean days per month ± SD (% change): **G1:** 0.33 ± 0.37 (121) **G2:** 0.11 ± 0.36 (42) **G3:** -0.04 ± 0.07 (-17) **G1 vs. BL:** p=0.003 **G2 vs. BL:** p=NS **G3 vs. BL:** p=NS **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR	**Overall quality:** Poor **Risk of bias:** Randomization: Low Allocation concealment:: Low Selective reporting: Low Blinding patients/personnel: High Blinding outcome assessment: Unclear Incomplete outcome reporting: High Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
RCT **Blinding:** None		**G1:** 29 **G2:** 30 **G3:** 15 16 week treatment period: **G1:** 24 **G2:** 22 **G3:** 13 16 week followup: **G1:** 21 **G2:** 18 **G3:** 11 **Age, mean years ± SD:** **G1**: 29.7 ± 4.3 **G2**: 30.2 ± 4.7 **G3**: 30.1 ± 4.2 **BMI, mean kg/m^2 ± SD:** **G1:** 29.1 ± 8.83 **G2:** 27.7 ± 6.44 **G3:** 26.8 ± 5.56 **BMI ≥30, n (%):** **G1:** 11/29 (38) **G2:** 11/30 (37) **G3:** 4/15 (27) **Parity:** NR **Race/ethnicity:** NR		**Additional interventions:** NR **Adverse events:**[c] Isolated redness and subsequent hematomas, n: **G1:** 3 **G2:** 0 **G3:** 0 Dizziness, n: **G1:** 1 **G2:** 0 **G3:** 0 Nausea, n: **G1:** 1 **G2:** 0 **G3:** 0	

Notes: [a] Details about needle placement given in text on pg E38; [b] All three groups of women received oral information about the benefits of regular physical exercise and were instructed to complete an exercise diary during weeks 1-32 of the study; [c] No long-term adverse events in G1 and no short-term or long-term adverse events in G2 and G3.

AUB KQ1 Evidence Table (Reference ID #76)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Karakus et al., 2009 **Country:** Turkey **Enrollment period:** August 2004 to April 2005 **Intervention setting:** Outpatient clinic **Funding:** NR **Author industry relationship disclosures:** NR **Study Design:** RCT **Blinding:** None	**Intervention:** Vaginal micronized progesterone (8% gel) 90 mg, every other evening from menstrual cycle day 17 to 27 **Comparator:** Dydrogesterone 10 mg orally twice daily for 10 days starting on cycle day 15 **Groups:** **G1:** Vaginal progesterone **G2:** Oral progesterone **Followup:** 3 cycles	**Inclusion criteria:** • Aged 35 to 45 years • No menopausal symptoms • Did not take hormone therapy • Diagnosed with dysfunctional uterine bleeding • No contraindication for progesterone or progestins • Endometrial thickness >5 mm by transvaginal ultrasound **Exclusion criteria:** Taking anticoagulants or antiprostaglandins Prefer hormonal contraceptive methods Known intolerance to progesterone or progestins **N at enrollment:** **G1:** 34 **G2:** 35 **N at followup:** **G1:** 27 **G2:** 27 **Age, mean years ± SD:** **G1:** 39.1 ± 3.6 **G2:** 39.6 ± 3.0 **BMI, mean kg/m^2 ± SD:**	Secretory endometrium in endometrial sample, n (%): **G1:** 8 (29.6) **G2:** 6 (22.2) **G1 vs. G2:** p=0.412	**Bleeding:** Irregular bleeding pattern,[a] n (%): First cycle: **G1:** 2 (7.4) **G2:** 5 (18.5) **G1 vs. G2:** p=0.42 Second cycle: **G1:** 3 (11.1) **G2:** 3 (11.1) **G1 vs. G2:** p=1.0 Third cycle: **G1:** 2 (7.4) **G2:** 4 (14.8) **G1 vs. G2:** p=0.67 Secretory endometrium in endometrial sample, n (%): **G1:** 24 (88.9) **G2:** 22 (81.5) **G1 vs. G2:** p=0.732 **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** Self-reported patient satisfaction with treatment, n (%): **G1:** 23 (85) **G2:** 21 (78) **G1 vs. G2:** p=0.491 **Fertility:**	**Overall quality:** Poor **Risk of bias:** Randomization: Low Allocation concealment: High Selective reporting: Unclear Blinding patients/personnel: High Blinding outcome assessment: Unclear Incomplete outcome reporting: High Other: Unclear

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		G1: 29.2 ± 5.4 **G2:** 30.3 ± 3.7 **G1 vs. G2:** p=0.371 **Gravidity, mean ± SD:** **G1:** 4.4 ± 2.1 **G2:** 4.8 ± 2.3 **G1 vs. G2:** p=0.584 **Parity, mean ± SD:** **G1:** 3.0 ± 1.4 **G2:** 3.6 ± 2.2 **G1 vs. G2:** p=0.209 **Race/ethnicity:** NR		NR **Time to conception:** NR **Additional interventions:** See comment[b] **Adverse events, n:** Groin pain: **G1:** 1 **G2:** 0 5-kg weight gain: **G1:** 1 **G2:** 0 Ovarian cyst: **G2:** 1 **G2:** 0	

Table Notes: [a] Regular bleeding: cycle length less than 35 days and no intermenstrual bleeding; [b] Oral estrogen added for n=1 in G2 because of 45-day menstrual delay.

AUB KQ1 Evidence Table (Reference ID #700)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Moghetti et al., 2000 **Country:** Italy **Enrollment period:** NR **Intervention setting:** Hospital clinic **Funding:** Grants from Italian Ministry of Higher Education and Scientific Research, and Regione de Veneto **Author industry relationship disclosures:** NR **Study Design:** RCT **Blinding:** Patients, investigators	**Intervention:** Oral metformin 500 mg once daily for first week; 500 mg twice a day for a second week; 500 mg three times a day for 24 weeks **Comparator:** Placebo **Groups:** **G1:** Metformin **G2:** Placebo **Followup:** 26 weeks	**Inclusion criteria:** Women aged 18 to 35 years • Polycystic ovary syndrome[a] Normal glucose tolerance Referred for menstrual abnormalities with or without hirsutism **Exclusion criteria:** See inclusion criteria **N at enrollment[b]:** **G1+G2:** 23 **N at followup:** **G1+G2:** 23 **Age, mean years ± SD:** **G1:** 23.9 ± 1.2 **G2:** 21.4 ± 1.4 **BMI, mean kg/m^2 ± SD:** **G1:** 27.1 ± 1.5 **G2:** 32.6 ± 1.1 **G1 vs. G2:** p<0.05 **Parity:** NR **Race/ethnicity:** NR	**Bleeding:** Severe oligomenorrhea (6 or fewer menses per year), n (%): **G1+G2:** 20 (87) Less severe menstrual irregularities, n (%): **G1+G2:** 3 (13) Androstenedione, mean nmol/l ± SD: **G1:** 12.5 ± 1.5 **G2:** 10.3 ± 0.7 Free testosterone, mean pmol/l ± SD: **G1:** 11.6 ± 1.8 **G2:** 10.7 ± 1.4	**Bleeding:** Menstrual frequency improvement, median (IQR):[c] **G1:** NR **G2:** NR **G1 vs. G2:** p=0.002[d] Menstrual pattern improved: **G1:** 5 **G2:** 0 Androstenedione, mean nmol/l ± SD: **G1:** 13.6 ± 2.1 **G2:** 10.7 ± 1.0 **G1 vs. G2:** p=0.74 Free testosterone, mean pmol/l ± SD: **G1:** 8.7 ± 1.5 **G2:** 10.4 ± 1.7 **G1 vs. G2:** p=0.04 **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR	**Overall quality:** Poor **Risk of bias:** Randomization: Unclear Allocation concealment: Unclear Selective reporting: Unclear Blinding patients/personnel: Low Blinding outcome assessment: Low Incomplete outcome reporting: Unclear Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				Additional interventions: NR	

Table Notes: [a] PCOS diagnosed by presence of hyperandrogenic chronic anovulation, after exclusion of Cushing's syndrome, late onset 21-hydroxylase deficiency, thyroid dysfunction, hyperprolactinemia or androgen secreting tumors; [b] The authors do not report how many subjects were randomized to treatment and placebo; [c] Results only displayed graphically in Figure 1 (pg. 142); [d] After controlling for baseline BMI and androstenedione.

AUB KQ1 Evidence Table (Reference ID #1777)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Oner and Muderris, 2011 **Country:** Turkey **Enrollment period:** March 2008 to April 2009 **Intervention setting:** University gynecologic endocrinology clinic **Funding:** NR **Author industry relationship disclosures:** NR **Study Design:** RCT **Blinding:** NR	**Intervention:** 1.5 g/day metformin (500 mg 3 times per day) **Comparator:** 1.8 g/day N-acetyl-cysteine (600 mg 3 times per day) **Groups:** **G1:** Metformin **G2:** N-acetyl-cysteine **Followup:** 24 weeks	**Inclusion criteria:** PCOS[a] with hirsutism and menstrual irregularity **Exclusion criteria:** Congenital adrenal hyperplasia, Cushing's syndrome or androgen secreting tumors, thyroid disease, hyperprolactinemia Diabetes mellitus or impaired glucose tolerance Use of drugs known to affect carbohydrate metabolism within 3 months preceding the study **N at enrollment:** **G1:** 50 **G2:** 50 **N at followup:** **G1:** 30 **G2:** 45 **Age, mean years ± SD:** **G1:** 22.6 ± 4.8 **G2:** 23.7 ± 4.4 **BMI, mean kg/m^2 ± SD:** **G1:** 24.3 ± 6.2 **G2:** 23.0 ± 4.6 **Parity:** NR **Race/ethnicity:**	**Menstrual cycle:** Regular, n (%): **G1:** 5 (17) **G2:** 13 (29) **G1 vs. G2:** p=NS Irregular, n (%): **G1:** 25 (83) **G2:** 32 (71) **G1 vs. G2:** p=NS	**Menstrual cycle:** Regular, n (%): **G1:** 14 (47) **G2:** 24 (53) **G1 vs. G2:** p=NS Irregular, n (%): **G1:** 16 (53) **G2:** 21 (47) **G1 vs. G2:** p=NS Restoration of menstrual regularity, n (%): **G1:** 9 (36) **G2:** 11 (34) **G1 vs. G2:** p=NS **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR **Adverse Events:**	**Overall quality:** Poor **Risk of bias:** Randomization: Unclear Allocation concealment: Unclear Selective reporting: Low Blinding patients/personnel: Unclear Blinding outcome assessment: Unclear Incomplete outcome reporting: High Other: Unclear

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		NR		Discontinued due to gastrointestinal side effects, n (%): **G1:** 2 (4) **G2:** NR	

Table Notes: [a] PCOS defined as presence of at least two of following three criteria: (1) oligo- or anovulation, (2) clinical and/or chemical signs of hyperandrogenism and/or (3) polycystic ovaries.

AUB KQ1 Evidence Table (Reference ID #1363)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Ornstein et al., 2011 **Country:** United States **Enrollment period:** NR **Intervention setting:** Hospital **Funding:** Long Island Jewish Medical Center Small Grants **Author industry relationship disclosures:** None **Study Design:** RCT **Blinding:** None	**Intervention:** Hypocaloric low fat diet **Comparator:** Carbohydrate restriction without caloric or fat targets **Groups:** **G1:** Low fat diet **G2:** Low carbohydrate diet **Followup:** 12 weeks	**Inclusion criteria:** Aged 12 to 22 years Postmenarche ≥2 years Diagnosed with PCOS BMI 85th percentile **Exclusion criteria:** Use of medications known to cause menstrual dysfunction or to affect insulin secretion or action Endocrinopathies including non-classic 21-hydroxylase deficiency, thyroid dysfunction, Cushing's syndrome, hyperprolactinemia, and diabetes mellitus Androgen-producing tumors Renal or hepatic disease Pregnancy **N at enrollment:** **G1:** 12 **G2:** 12 **N at followup:** **G1:** 7 **G2:** 9 Age, mean ± SD years: **G1+G2:** 15.8 ± 2.2 **BMI:** NR **Parity:** NR	Cycle changes, mean ± SD: **G1+G2:** 0.6 ± 0.6 Weight, mean kg ± SD: **G1+G2:** 95.1 ± 18.6 Waist circumference, mean cm ± SD: **G1+G2:** 103.3 ± 12.3 BMI, kg/m^2 ± SD: **G1+G2:** 35.7 ± 6	Cycle changes, mean ± SD: **G1+G2:** 1.6 ± 1.3, **G1+G2 vs. BL:** p=0.003 Weight , mean kg ± SD: **G1+G2:** 89 ± 18 **G1+G2 vs. BL:** p<0.0001 Waist circumference, mean cm ± SD: **G1+G2:** 97.6 ± 13 **G1+G2 vs. BL:** p=0.01 BMI, kg/m^2 ± SD: **G1+G2:** 32.9 ± 5.8 **G1+G2 vs. BL:** p<0.0001 **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR **Adverse Events:** NR	**Overall quality:** Poor **Risk of bias:** Randomization: Unclear Allocation concealment: Unclear Selective reporting: Low Blinding patients/ personnel: High Blinding outcome assessment: Unclear Incomplete outcome reporting: High Other: High

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		Race/ethnicity, n (%): White (non Latina): **G1+G2:** 8 (50) Latina: **G1+G2:** 3 (19) Black: **G1+G2:** 2 (13) South Asian: **G1+G2:** 2 (13) Asian: **G1+G2:** 1 (6)			

AUB KQ1 Evidence Table (Reference ID #1675)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Paoletti et al., 1996 **Country:** Italy **Enrollment period:** NR **Intervention setting:** Clinic **Funding:** NR **Author industry relationship disclosures:** NR **Study Design:** RCT **Blinding:** Subjects, investigators	**Intervention:** Cabergoline, one 0.5 mg tablet every week for ≥4 months **Comparator:** Placebo **Groups:** **G1:** Cabergoline **G2:** Placebo **Ga:** Polycystic ovary syndrome **Gb:** Control **Followup:** 4 cycles	**Inclusion criteria:** • Aged 20 to 28 years • Lean polycystic ovary syndrome: persistent amenorrhea or oligomenorrhea of perimenarchal onset • Controls were healthy women with: regular menstrual cycles **Exclusion criteria:** See inclusion criteria **N at enrollment:** **G1a:** 8 **G1b:** 8 **G2a:** 6 **G2b:** 7 **N at followup:** **G1a:** 8 **G1b:** 8 **G2a:** 6 **G2b:** 7 **Age, years mean ± SD:** **Ga:** 22 ± 3 **Gb:** 23 ± 2 **BMI, mean kg/m^2 ± SD:** **Ga:** 22.9 ± 0.29 **Gb:** 22.7 ± 0.38 **Parity:** NR **Race/ethnicity:** NR	**Menstrual cycle:** Oligomenorrhea, n: **G1a:** 3/8 **G2a:** 3/6 Amenorrhea, n: **G1a:** 5/8 **G2a:** 3/6	**Menstrual cycle:** Regular cycles,[a] n: **G1a:** 3/8 **G2a:** 0/6 Spontaneous menses within 32 to 37 days from onset of treatment, n: **G1a:** 5/8 **G2a:** 0/6 Persistent oligomenorrhea, n: **G2a:** 3/6 Persistent amenorrhea, n: **G2a:** 3/6 **Quality of life:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR	**Overall quality:** Good **Risk of bias:** Randomization: Low Allocation concealment: Unclear Selective reporting: Low Blinding patients/personnel: Low Blinding outcome assessment: Low Incomplete outcome reporting: Low Other: Low

Table Notes: [a] 28-day intervals.

AUB KQ1 Evidence Table (Reference ID #1783)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Abu Hashim et al., 2011 **Country:** Egypt **Enrollment period:** July 2008 to September 2010 **Intervention setting:** University outpatient clinic and private practice **Funding:** None. NuvaRing provided by Organon Egypt and sanitary pads by Proctor and Gamble, Cairo, Egypt **Author industry relationship disclosures:** NR **Study Design:** RCT **Blinding:** Outcome assessors (laboratory and statistical)	**Intervention:** Nuvaring, 15 mcg of ethinyl estradiol and 120 mcg of etonogestrel; inserted between days 1-5 of cycle for three weeks followed by one week ring free. **Comparator:** Norethisterone acetate tablets 5 mg three times daily from days 5-26 of cycle for three cycles **Groups:** **G1:** Vaginal ring **G2:** Norethisterone **Followup:** 3 months	**Inclusion criteria:** Heavy menstrual bleeding (mean PBAC score >185 for two control cycles) Parous women desiring contraception Age 20-35 Good general health with regular menstrual cycle and evidence of ovulation Normal pelvic exam with uterus < 10 cm No pathology identified in pelvic ultrasound, normal histology on endometrial biopsy, negative cervical smear No contraindication to either contraceptive vaginal ring or norethisterone **Exclusion criteria:** Pregnancy BMI >30 kg/m^2 Smokers Current IUD use AUB not fully investigated Hormone therapy or any medication that might affect MBL within previous three months Used injectable hormones for contraception	**Bleeding:** PBAC, mean score ± SD: **G1:** 287.8 ± 77.4 **G2:** 302.4 ± 84.6 Cycle length, mean days ± SD: **G1:** 26.9 ± 3.7 **G2:** 27.2 ± 4.4 Menses duration, mean days ± SD: **G1:** 8.8 ± 2.7 **G2:** 8.4 ± 2.6 Hemoglobin, g/dL ± SD: **G1:** 10.5 ± 1.3 **G2:** 10.7 ± 1.2 Ferritin (mcg/dL) **G1:** 18.4 ± 3.3 **G2:** 17.1 ± 2.9 **Quality of life:** Self-rated health ≥ very good, n (%): **G1:** 2 (4.1) **G2:** 2 (4.2) Feeling physically unwell, mean number of days ± SD: **G1:** 7.4 ± 1.8 **G2:** 7.5 ± 2.1 Feeling mentally unwell, mean number of days ± SD: **G1:** 5.8 ± 1.7 **G2:** 6.2 ± 1.6 No regular activity, mean	**Bleeding:** PBAC, mean score ± SD: **G1:** 90.2 ± 24.4 **G2:** 92.3 ± 26.7 **G1 vs. G2:** p=NS **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.001 PBAC score reduction from baseline, (%): **G1:** 68.6 **G2:** 69.5 **G1 vs. G2:** p=NS Menses duration, mean days ± SD: **G1:** 5.3 ± 1.2 **G2:** 5.5 ± 1.1 **G1 vs. G2:** p=NS **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.001 Hemoglobin, g/dL ± SD: **G1:** 11.3 ± 1.2 **G2:** 11.4 ± 1.1 **G1 vs. G2:** p=NS **G1 vs. BL:** p=0.02 **G2 vs. BL:** p=0.03 Ferritin (mcg/dL) **G1:** 36.7 ± 6.2 **G2:** 35.1 ± 5.7 **G1 vs. G2:** p=NS **G1 vs. BL:** p=0.01 **G2 vs. BL:** p=0.01 **Quality of life:** Self-rated health ≥ very good, n (%):	**Overall quality:** Fair **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Low Blinding patients/personnel: High Blinding outcome assessment: High Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		previous 12 months Use of drugs that interfere with contraceptive hormone metabolism Previous endometrial resection/ablation and other pathology Heavy menstrual bleeding of endocrine or systemic origin **N at enrollment:** **G1:** 48 **G2:** 47 **N at followup:** **G1:** 48 **G2:** 47 **Age, mean years ± SD:** **G1:** 27.8 ± 4.9 **G2:** 28.2 ± 4.4 **BMI, mean kg/m^2 ± SD:** **G1:** 24.8 ± 3.8 **G2:** 25.4 ± 3.2 **Parity, n (%):** 1 **G1:** 5 (10.4) **G2:** 6 (12.8) 2 **G1:** 14 (29.2) **G2:** 10 (21.3) ≥ 3 **G1:** 29 (60.4) **G2:** 31 (65.9) NR **Race/ethnicity:**	number lost days ± SD: **G1:** 6.4 ± 2.1 **G2:** 6.3 ± 2.3	**G1:** 17 (35.4) **G2:** 14 (29.7) **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.001 Feeling physically unwell, mean number of days ± SD: **G1:** 3.3 ± 1.1 **G2:** 3.5 ± 1.3 **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.001 Feeling mentally unwell, mean number of days ± SD: **G1:** 4.7 ± 1.2 **G2:** 5.1 ± 1.3 **G1 vs. BL:** p=NS **G2 vs. BL:** p=NS No regular activity, mean number of lost days ± SD: **G1:** 1.7 ± 1.2 **G2:** 2.6 ± 1.4 **G1 vs. BL:** p=0.002 **G2 vs. BL:** p=0.03 **Pain:** NR **Sexual function:** NR **Patient satisfaction:** Very satisfied/satisfied, n (%): **G1:** 34 (70.8) **G2:** 20 (42.5) **G1 vs. G2:** p=0.003 Uncertain/dissatisfied, n	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		NR		(%): **G1:** 14 (33.4) **G2:** 27 (57.5) **G1 vs. G2:** p=0.003 Continued treatment, n (%): **G1:** 37 (77) **G2:** 12 (25.5) **G1 vs. G2:** p=0.001 Discontinued treatment, n (%): **G1:** 11 (23) **G2:** 35 (74.5) **G1 vs. G2:** p=0.001 **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR **Adverse Events:** Nausea, n (%): **G1:** 1 (2) **G2:** 2 (4.2) **G1 vs. G2:** p=NS Headache, n (%): **G1:** 3 (6.25) **G2:** 2 (4.2) **G1 vs. G2:** p=NS Breast tenderness, n (%): **G1:** 2 (4.2) **G2:** 3 (6.4) **G1 vs. G2:** p=NS Breakthrough bleeding/spotting, n (%): **G1:** 2 (4.2) **G2:** 6 (12.8) **G1 vs. G2:** p=0.02	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				Leukorrhea, n (%): **G1:** 5 (10.4) **G2:** 1 (2.1) **G1 vs. G2:** p=0.01 Vaginal discomfort, n (%): **G1:** 2 (4.2) **G2:** NA **G1 vs. G2:** p=0.003 Vaginitis, n (%): **G1:** 4 (8.3) **G2:** 1 (2.1) **G1 vs. G2:** p=0.03 Ring-related events, n (%): **G1:** 3 (6.25) **G2:** NA p=0.002	

AUB KQ1 Evidence Table (Reference ID #1170)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Andersch et al., 1988 **Country:** Sweden **Enrollment period:** NR **Intervention setting:** NR **Funding:** University of Goteborg and The Goteborg Medical Society **Author industry relationship disclosures:** NR **Study Design:** RCT (crossover) **Blinding:** NR	**Intervention:** Flurbiprofen 100 mg, 2 times per day on days 1-5 for cycles 3 and 4 followed by tranexamic acid for cycles 5 and 6 **Comparator:** Oral tranexamic acid 1.5 g, 3 times per day on days 1-3; 1 g twice daily on days 4 and 5 for cycles 3 and 4 followed by flurbiprofen for cycles 5 and 6 **Groups:** **G1:** Flurbiprofen first then tranexamic acid **G2:** Tranexamic acid first then flurbiprofen **Ga:** Flurbiprofen **Gb:** Tranexamic acid **Followup:** 6 months[a]	**Inclusion criteria:** • Idiopathic menorrhagia MBL >80 ml during 2 periods No history or evidence of pelvic pathology **Exclusion criteria:** Menorrhagia caused by uterine myomata Menorrhagia caused by intrauterine device Use of oral contraceptives or intrauterine device Pregnancy in previous 6 months **N at enrollment:** **G1+G2:** 15 **N at followup:** **G1+G2:** 15 **Age, mean years (range):** **G1+G2:** 40.5 (34, 49) **BMI:** NR **Parity, mean (range):** **G1+G2:** 1.7 (0, 3) **Race/ethnicity:** NR	**Bleeding:** MBL measured using the alkaline hematin method, mean ml (SE) (range): **G1+G2:** 295 (52) (81, 701) Hemoglobin, mean g/l (SE): **G1+G2:** 127.4 (3.7)	**Bleeding:** MBL measured using the alkaline hematin method, mean ml (SE) (range): **Ga:** 223 (44) (50, 636) **Gb:** 155 (33) (36, 511) MBL change from baseline, %, p-value: **Ga:** -24, p<0.01 **Gb:** -53, p< 0.01 **Ga vs. Gb:** p<0.01 Hemoglobin, mean g/l (SE), p value: **Ga:** 127.1 (3.4), p=ns **Gb:** 126.2 (3.0), p=ns **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NA **Additional interventions:** NR **Adverse events[b]:**	**Overall quality:** Poor **Risk of bias:** Randomization: Unclear Allocation concealment: Unclear Selective reporting: Unclear Blinding patients/personnel: Unclear Blinding outcome assessment: Unclear Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				Patient complained of side effects which they attributed to medication, n: **Ga:** 7 **Gb:** 4 Vomiting and difficulty swallowing, n: **Ga:** NR **Gb:** 3	

Table Notes: [a] Cycles 1 and 2 Control –no treatment followed by 4 treatment cycles (cross over after 4th cycle); [b] "Treatment with tranexamic acid caused nausea, dizziness, numbness, “restless legs”, headache and in 3 women vomiting and difficulty swallowing. Flurbiprofen caused tiredness, stomach pains and nausea. No patient discontinued therapy due to side effects."

AUB KQ1 Evidence Table (Reference ID #871)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Bonnar and Sheppard, 1996 **Country**: Ireland **Enrollment period**: NR **Intervention setting**: University department of OB-GYN **Funding**: Health Research Board of Ireland and Pharmacia, Sweden **Author industry relationship disclosures:** None **Study Design:** RCT **Blinding**: None	**Intervention/ Comparator:** Tranexamic acid 1 g six hourly; mefenamic acid 500 mg eight hourly; ethamsylate 500 mg six hourly All treatments taken for five days from day 1 of bleeding for three cycles **Groups:** **G1:** Tranexamic acid **G2:** Mefenamic acid **G3:** Ethamsylate **Followup:** 3 cycles	**Inclusion criteria:** • Aged 35 to 46 years • Complaint of regular heavy menstrual bleeding Mean menstrual loss >80 ml measured over three consecutive menstrual periods before treatment **Exclusion criteria:** Organic causes of menorrhagia excluded by hysteroscopy, endometrial biopsy, cervical smear test 3 to 12 months before enrollment History of renal or hepatic impairment Previous thromboembolic disease Inflammatory bowel disease Peptic or intestinal ulceration Coagulation or fibrinolytic disorders **N at enrollment:** **G1:** 27 **G2:** 25 **G3:** 29 **N at followup:** **G1:** 26	**Bleeding:** MBL measured by alkaline hematin method during 3 cycles pretreatment, mean ml: **G1:** 164 **G2:** 186 **G3:** 170 MBL duration, mean days ± SD: **G1:** 5.5 ± 1.4 **G2:** 5.8 ± 1.3 **G3:** 5.7 ± 1.1 Sanitary towels, mean ± SD: **G1:** 23 ± 7.0 **G2:** 25 ± 7.0 **G3:** 25 ± 9.0	**Bleeding:** MBL measured by alkaline hematin method during 3 treatment cycles, mean ml: **G1:** 75 **G2:** 148 **G3:** 175 MBL change, n (%): Less: **G1:** 18 (69) **G2:** 13 (57) **G3:** 12 (44) Same: **G1:** 4 (15) **G2:** 5 (22) **G3:** 5 (19) Greater: **G1:** 4 (15) **G2:** 4 (17) **G3:** 8 (30) Dysmenorrhea change, n (%): Better: **G1:** 5 (19) **G2:** 3 (13) **G3:** 1 (4) Same: **G1:** 14 (54) **G2:** 11 (48) **G3:** 19 (70) Worse: **G1:** 7 (27) **G2:** 8 (35) **G3:** 4 (15) MBL duration, mean	**Overall quality:** Poor **Risk of bias:** Randomization: Low Allocation concealment: Unclear Selective reporting: Unclear Blinding patients/personnel: High Blinding outcome assessment: High Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		G2: 23 **G3:** 27 **Age, mean years ± SD:** **G1:** 40 ± 5 **G2:** 38 ± 8 **G3:** 37 ± 8 **BMI:** NR **Height, mean cm ± SD:** **G1:** 160 ± 6 **G2:** 161 ± 6 **G3:** 164 ± 7 **Weight, mean kg ± SD:** **G1:** 66 ± 10 **G2:** 66 ± 12 **G3:** 64 ± 9 **Parity:** NR **Race/ethnicity:** NR		days ± SD: **G1:** 4.9 ± 1.8 **G2:** 5.3 ± 1.3 **G3:** 5.7 ± 2.0 Sanitary towels, mean ± SD, p value: **G1:** 20 ± 6.0, p<0.01 **G2:** 23 ± 9.0, p<0.05 **G3:** 25 ± 9.0 **G1 vs. BL:** p<0.01 **G2 vs. BL:** p<0.05 **G3 vs. BL:** p=NS **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** Wish to continue treatment at end of study, n (%): **G1:** 20 (77) **G2:** 17 (74) **G3:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				Adverse events: Withdrawal,[a] n: **G1:** 4 **G2:** 3 **G3:** 11 Withdrawal due to unwanted event such as nausea, headache or dizziness, n: **G1:** 3 **G2:** 1 **G3:** 4	

Table Notes: [a] Reasons for withdrawal: poor efficacy (G3: n=5; G2: n=1); unwanted event such as nausea, headache and dizziness (G1: n=3; G2: n=1; G3: n=4).

AUB KQ1 Evidence Table (Reference ID #1116)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Cameron et al., 1990 **Country:** United Kingdom **Enrollment period:** NR **Intervention setting:** Outpatient department **Funding:** Parke-Davis Research Laboratories, Eastleigh, UK **Author industry relationship disclosures:** NR **Study Design:** RCT **Blinding:** NR	**Intervention:** Mefenamic acid, 500 mg three times daily on days 1-5 of menses **Comparator:** Norethisterone, 5 mg twice daily on cycle days 19-26 **Groups:** **G1:** Mefenamic acid **G2:** Norethisterone 2 control cycles Cycle 1 Cycle 2 2 treatment cycles Cycle 3 Cycle 4	**Inclusion criteria:** Heavy menstruation defined by average MBL >80 ml per cycle **Exclusion criteria:** Organic disease Receiving medical treatment for menorrhagia **N at enrollment:** **G1:** 17 **G2:** 15 **N at followup:** **G1:** 17 **G2:**15 **Age, median years (range):** **G1:** 40 (27, 48) **G2:** 40 (21, 51) **BMI:** NR **Height, median cm (range):** **G1:** 163 (154, 177) **G2:** 163 (150, 181) **Weight, median kg (range):** **G1:** 67 (52, 92) **G2:** 65 (48, 102) **Parity:** NR	**Bleeding:** MBL measured by alkaline hematin method, median ml (range): **G1:** 123 (86, 237) **G2:** 109 (81, 236) Duration at cycle 1, median days (range): **G1:** 7 (5, 8) **G2:** 7 (5, 10) Duration at cycle 2, median days (range): **G1:** 6 (4, 9) **G2:** 6 (4, 9) Cycle length at cycle 1, median days (range): **G1:** 28 (21, 35) **G2:** 28 (21, 35) Cycle length at cycle 2, median days (range): **G1:** 27 (21, 33) **G2:** 29 (21, 31**)**	**Bleeding:** MBL measured by alkaline hematin method, median ml (range): **G1:** 81 (22, 193) **G2:** 92 (43, 189) **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.002 MBL change, median % (range): **G1:** -24 (-83, 5) **G2:** -20 (-53, 2) **G1 vs. G2:** p>0.1 Duration at cycle 3, median days (range): **G1:** 6 (5, 9) **G2:** 6 (4, 8) Duration at cycle 4, median days (range): **G1:** 5 (3, 8) **G2:** 6 (4, 8) **G1 vs. BL:** p<0.01 **G2 vs. BL:** p=NS Cycle length at cycle 3, median days (range): **G1:** 27 (25, 37) **G2:** 29 (28, 32) Cycle length at cycle 4, median days (range): **G1:** 28 (25, 32) **G2:** 29 (26, 35) **G1 vs. BL:** p=NS **G2 vs. BL:** p=NS **Quality of life:**	**Overall quality:** Poor **Risk of bias:** Randomization: Unclear Allocation concealment: Unclear Selective reporting: Low Blinding patients/personnel: Unclear Blinding outcome assessment: Unclear Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		Race/ethnicity: NR		NR **Pain, n (%):** Abdominal pain: **G1:** 3 (18) **G2:** 3 (20) Headache: **G1:** 4 (24) **G2:** 5 (33) **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR **Adverse events, n (%):** Any side effect: **G1:** 10 (59) **G2:** 9 (60) Nausea: **G1:** 2 (12) **G2:** 1 (7) Other[a]: **G1:** 2 (12) **G2:** 1 (7)	

Table Notes: [a] Not including abdominal pain or headache.

AUB KQ1 Evidence Table (Reference ID #1184)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Cameron et al., 1987 **Country:** United Kingdom **Enrollment period:** NR **Intervention setting:** Hospital **Funding:** Birthright research grant, Royal College of Obstetricians and Gynaecologists **Author industry relationship disclosures:** NR **Study Design:** RCT **Blinding:** NR	**Intervention:** Mefenamic acid 500 mg three times per day for the first five days of cycle; **Comparator:** Norethisterone 5 mg two times per day on cycle days 15 to 25; Progesterone-impregnated coil releasing 65 mcg progesterone daily Two control cycles, two treatment cycles **Groups[a]:** **G1:** Mefenamic acid **G2:** Norethisterone **G3:** Progesterone-impregnated coil **Followup:** 4 months	**Inclusion criteria:** Mean MBL >50 ml **Exclusion criteria:** See inclusion criteria **N at enrollment:** **G1:** 8 **G2:** 8 **G3:** 8 **N at followup:** **G1:** 6 **G2:** 7 **G3:** 6 **Age, median years (range):** **G1:** 40 (33, 48) **G2:** 39 (35, 46) **G3:** 40 (29, 42) **BMI:** NR **Weight, median kg (range):** **G1:** 64 (50, 70) **G2:** 64 (52, 73) **G3:** 70 (54, 89) **Height, median cm (range):** **G1:** 162 (149, 164) **G2:** 164 (152, 169) **G3:** 162 (145, 164) **Parity, median (range):** **G1:** 4 (2, 4)	**Bleeding:** MBL measured by alkaline hematin method, median ml (range): **G1:** 68 (61, 169) **G2:** 94 (55, 312) **G3:** 71 (56, 164) MBL measured by alkaline hematin method, followup group, median ml (range): **G1:** 85 (68, 169) **G2:** 131 (55, 259) **G3:** 64 (56, 164) Number of bleeding days, median (range): **G1:** 5 (4, 7) **G2:** 6 (4, 7) **G3:** 5 (4, 6) Cycle length, median days (range): **G1:** 28 (23, 38) **G2:** 28 (24, 30) **G3:** 26 (23, 30) Endometrial prostaglandin, median pg/mg (range): **G1:** 412 (256, 9506) **G2:** 770 (152, 2251) **G3:** 842 (265, 1630)	**Bleeding:** MBL measured by alkaline hematin method, median ml (range): **G1:** 47 (39, 210) **G2:** 110 (24, 222) **G3:** 45 (31, 77) **G1 vs. BL:** p=0.05 **G2 vs. BL:** p=NS **G3 vs. BL:** p<0.05 Number of bleeding days: No difference vs. baseline[b] Endometrial prostaglandin, median pg/mg (range): **G1:** 546 (412, 3434) **G2:** 985 (55, 1987) **G3:** 273 (178, 832) **G1 vs. BL:** p=NS **G2 vs. BL:** p=NS **G3 vs. BL:** p=0.05 **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR	**Overall quality:** Poor **Risk of bias:** Randomization: Unclear Allocation concealment: Unclear Selective reporting: Unclear Blinding patients/personnel: High Blinding outcome assessment: High Incomplete outcome reporting: Unclear Other: Unclear

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		G2: 4 (1, 4) **G3:** 2 (2, 4) **Race/ethnicity:** NR		**Additional interventions:** NR **Adverse events:** NR	

Table Notes: [a] Does not include a treatment group randomized to danazol (n=6); [b] Baseline refers to control cycles.

AUB KQ1 Evidence Table (Reference ID #123)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Endrikat et al., 2009 **Country:** Canada **Enrollment period:** NR **Intervention setting:** 9 centers **Funding:** Bayer Schering Pharma AG, Berlin, Germany **Author industry relationship disclosures:** 5/6 **Study Design:** RCT **Blinding:** Open-label	**Intervention:** LNG-IUS 52 mg levonorgestrel released up to 20 µg per 24 hours inserted within 7 days of start of last menstrual period for 12 months **Comparator:** One tablet daily for 12 months of COC containing 1 mg norethindrone acetate and 20 µg ethinyl estradiol for days 1-21 and placebo tablet for days 22-28 **Groups:** **G1:** LNG-IUS **G2:** COC **Followup:** 12 months	**Inclusion criteria:** Aged ≥30 years Healthy • Diagnosis of idiopathic menorrhagia assessed by MBL score ≥100 on PBLAC for two consecutive cycles Normal or only slightly enlarged uterus **Exclusion criteria:** Contraindications for LNG-IUS and COC use Metabolic and endocrine diseases Diagnostically unclassified genital bleeding History of liver or vascular disease Concomitant use of medications that could influence study objective, including: sex steroids; tranexamic acid; NSAIDs; platelet aggregation inhibitors; anticoagulants; and drugs known to induce or inhibit liver enzymes Intramural or subserous fibroids of mean diameter ≥4 cm or submucous fibroids Adenomyosis or endometrial abnormalities (e.g., polyps or hyperplasia) Perimenopausal **N at enrollment:** **G1:** 20 **G2:** 19	**Bleeding:** MBL measured by PBLAC score, median: **G1:** 228 **G2:** 290 Hemoglobin,[a] mean g/L: **G1:** 126 **G2:** 125	**Bleeding:** MBL measured by PBLAC score at 12 months, median: **G1:** 13 **G2:** 72 **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.001 **G1 vs. G2:** p=0.002 MBL measured by PBLAC score at 12 months, estimate for median difference (95% CI): **G1 vs. G2:** -62 (-89, -18) MBL measured by PBLAC score at 12 months, mean % change: **G1:** -83 **G2:** -68 Treatment success,[b] n (%): **G1:** 16/20 (80.0) **G2:** 7/19 (36.8) **G1 vs. G2:** p<0.009 Hemoglobin at 12 months, mean g/L: **G1:** 134 **G2:** 136 Hemoglobin at 12 months, baseline-adjusted mean g/L change: **G1:** +8.6 **G2:** +9.6 **G1 vs. G2:** p=0.711	**Overall quality:** Poor **Risk of bias:** Randomization: Low Allocation concealment: High Selective reporting: Low Blinding patients/personnel: High Blinding outcome assessment: Unclear Incomplete outcome reporting: Low Other: High

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		N at followup: **G1:** 17 **G2:** 12 **Time since start of menorrhagia, mean years ± SD:** **G1:** 10.0 ± 8.23 **G2:** 6.1 ± 4.4 **Age, mean years ± SD:** **G1:** 41.8 ± 4.3 **G2:** 42.4 ± 4.4 **BMI, mean kg/m^2 ± SD** **G1:** 24.3 ± 1.9 **G2:** 22.6 ± 2.3 **Births, n (%)** 0: **G1:** 3 (15.0) **G2:** 3 (15.8) 1: **G1:** 6 (30.0) **G2:** 4 (21.1) 2: **G1:** 6 (30.0) **G2:** 10 (52.6) ≥3: **G1:** 5 (25.0) **G2:** 2 (10.5) **Race/ethnicity:** NR		Hemoglobin, estimate for mean difference (95% CI): **G1 vs. G2:** -0.99 (-6.43, 4.45) **Quality of life:** Menorrhagia severity score[c]: 6 months: **G1:** NR **G2:** NR **G1 vs. G2:** p=0.045 12 months: **G1:** NR **G2:** NR **G1 vs. G2:** p=NS Menorrhagia severity score, estimated mean % difference at 6 months (95% CI): **G1 vs. G2:** -6.37[d] (-12.61, -0.14) **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				Adverse events: Discontinued study (reasons were intermenstrual bleeding, menstrual disorder, and headache), n: **G1:** 1 **G2:** 5	

Table Notes: [a] Hemoglobin analyzed in the sub-population who had not used iron supplements during the study. Results were similar to whole study population (data not shown); [b] Treatment success defined as MBL score < 100 at 12 months; treatment failure recorded if MBL score ≥ 100 or if treatment was discontinued; [c] Assessed by condition specific questionnaire (see: Ruta et al.) but scores only displayed graphically; [d] Menorrhagia severity scores significantly lower (better quality of life) in G1 compared to G2 at 6 months.

AUB KQ1 Evidence Table (Reference ID #1349)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Fraser et al., 2011 **Country:** Australia, Europe **Enrollment period:** February 2006 to May 2008 **Intervention setting:** 34 centers **Funding:** Bayer Health Care Pharmaceuticals **Author industry relationship disclosures:** 7/7 **Study Design:** RCT **Blinding:** Patients, investigators	**Intervention:** Estradiol valerate/ dienogest, oral 7 consecutive treatment cycles of 28 days each (estradiol valerate 3 mg on days 1-2, estradiol valerate 2 mg /dienogest 2 mg on days 3-7, estradiol valerate 2 mg/ dienogest 3 mgs on days 8-24, estradiol valerate 1 mg on days 25-26, placebo on days 27-28) **Comparator:** Placebo **Groups:** **G1:** Estradiol valerate/dienogest **G2:** Placebo **Followup:** 8 months	**Inclusion criteria[a]:** Aged 18 or older Heavy menstrual bleeding Two or more menstrual bleeding episodes with a MBL of >80 ml, prolonged menstrual bleeding (≥8 days) and/or frequent menstrual bleeding (>5 episodes with a minimum of 20 bleeding days overall) during the 90 day run-in phase Willing to use barrier method of contraception Normal endometrial biopsy result or mild, simple endometrial hyperplasia 6 months prior to study entry **Exclusion criteria:** Abnormal transvaginal ultrasound Abnormal lab values which were clinically significant History of endometrial ablation Dilatation and curettage 2 months preceding the study Bleeding due to organic pathology determined during 90 day run-in phase including chronic endometriosis, adenomyosis, endometriosis, endometrial polyps,	**Bleeding:** MBL measured by the alkaline hematin method, mean ml ± SD: **G1:** 639.4 + 513.5 **G2:** 645.1 + 391.2 Bleeding and spotting days, 90-day run-in phase, mean: **G1:** 23.0 **G2:** 21.0 Bleeding only days, 90-day run-in phase, mean ± SD: **G1:** 17.3 ± 6.7 **G2:** 16.6 ± 6.7 Spotting only days, 90-day run-in phase, mean ± SD: **G1:** 5.7 ± 5.6 **G2:** 4.4 ± 5.1 Bleeding episodes, 90-day run-in phase, mean ± SD: **G1:** 3.5 ± 0.6 **G2:** 3.4 ± 0.7 Sanitary protection items, 90-day run-in phase, mean ± SD: **G1:** 81.6 ± 32.7 **G2:** 82.0 ± 39.3 Hemoglobin, mean g/dl ± SD: **G1:** 12.1 ± 1.2 **G2:** 12.1 ± 1.4 Hematocrit, mean % ± SD: **G1:** 39.7 ± 3.7 **G2:** 39.8 ± 4.2	**Bleeding:** MBL measured by the alkaline hematin method, mean ml ± SD: **G1:** 175.8 ± 200.8 **G2:** 553.6 + 308.0 MBL measured by the alkaline hematin method, mean change[d] ml ± SD: **G1:** -485 ± 409.6 **G2:** -93.2 ± 268.0 **G1 vs. G2:** p<0.0001 MBL < 80 ml for each episode, n (%): **G1:** 86/136 (63.2) **G2:** 11/76 (14.5) Bleeding and spotting days, 90-day efficacy phase, mean: **G1:** 21.3 **G2:** 19.1 Bleeding and spotting days, mean change[d]: **G1:** -1.6 **G2:** -1.9 Bleeding only days, 90-day efficacy phase, mean ± SD: **G1:** 13.7 ± 7.0 **G2:** 14.9 ± 5.7 Bleeding only days, mean change[d] ± SD: **G1:** -3.7 ± 8.4 **G2:** -2.1 ± 7.2	**Overall quality:** Good **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Unclear Blinding patients/personnel: Low Blinding outcome assessment: Low Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		leiomyomas or uterine malignancy Unwilling to discontinue tranexamic acid or NSAIDs during menses BMI >32 kg/m^2 Women aged 35 or older who smoked more than 10 cigarettes per day (or any number of cigarettes in Australia and the UK) Contraindications to the use of combined oral contraceptives **N at enrollment:** **G1:** 149 **G2:** 82 **N at followup:** **G1:** 109 **G2:** 62 **Age, mean years ± SD:** **G1:** 39.5 ± 6.6 **G2:** 38.5 ± 7.5 **BMI, mean kg/m^2 ± SD:** **G1:** 24.6 ± 3.5 **G2:** 25.7 ± 3.0 **Weight, mean kg ± SD:** **G1:** 69.8 ± 11.8 **G2:** 71.6 ± 10.2 **Parity:** NR **Race/ethnicity, n (%):** Caucasian: **G1:** 144 (96.6)	Ferritin, mean ng/ml ± SD: **G1:** 13.6 ± 13.6 **G2:** 13.9 ± 14.5	**G1 vs. G2:** p=0.0186 Spotting only days, 90-day efficacy phase, mean ± SD: **G1:** 7.6 ± 7.8 **G2:** 4.2 ± 5.5 Spotting only days, mean change[d] ± SD: **G1:** 2.1 ± 8.2 **G2:** -0.2 ± 6.0 Bleeding episodes, 90-day efficacy phase, mean ± SD: **G1:** 3.1 ± 0.9 **G2:** 3.1 ± 0.6 Bleeding episodes, mean change[d] ± SD: **G1:** -0.4 ± 1.1 **G2:** -0.4 ± 0.7 **G1 vs. G2**: p=0.5095 Sanitary protection items, 90-day efficacy phase, mean ± SD: **G1:** 43.3 ± 31.7 **G2:** 64.8 ± 26.3 Sanitary protection items, mean change[d] ± SD: **G1:** -38.4 ± 30.0 **G2:** -16.5 ± 32.2 **G1 vs. G2**: p<0.0001 Reduction in MBL volume, mean % (median): **G1:** 69.4 (79.2) **G2:** 5.8 (7.4)	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		G2: 80 (97.6) Black: **G1:** 1 (0.7) **G2:** 0 (0) Asian: **G1:** 2 (1.3) **G2:** 1 (1.2) Other: **G1:** 2 (1.3) **G2:** 1 (1.2) **Bleeding symptoms,[b] n (%):** Prolonged bleeding: **G1:** 20 (13.4) **G2:** 10 (12.2) Frequent bleeding: **G1:** 0 **G2:** 0 Heavy bleeding: **G1:** 136 (91.3) **G2:** 76 (92.7)		**G1 vs. G2:** p<0.0001 ≥20% reduction in MBL,%: **G1:** 94 **G2:** 40 ≥50% reduction in MBL,%: **G1:** 84 **G2:** 12 ≥80% reduction in MBL,%: **G1:** 50 **G2:** 0 Hemoglobin, adjusted change from baseline, mean g/dl: **G1:** +0.70 **G2:** +0.05 **G1 vs. G2:** p<0.0001 Hematocrit, adjusted change from baseline, mean %: **G1:** +1.5 **G2:** -0.05 **G1 vs. G2**: p<0.0049 Ferritin, adjusted change from baseline, mean ng/ml: **G1:** +8.6 **G2:** +0.4 **G1 vs. G2**: p<0.0017 Patient reported improvement in bleeding symptoms, %: **G1:** 77.9 **G2:** 45.1 **G1 vs. G2:** p<0.0001	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				Responder status,[c] n (%): Complete: **G1:** 44 (29.5) **G2:** 1 (1.2) Partial or non-responder[e]: **G1:** 64 (43.0) **G2:** 61 (74.4) Missing data: **G1:** 41 (27.5) **G2:** 20 (24.4) Complete response rate (excluding patients with missing data), % (95% CI): **G1:** 40.7 (31.4, 50.6) **G2:** 1.6 (0.0, 8.7) **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions:** Concomitant use of iron, n (%): **G1:** 28/149 (18.8) **G2:** 27/82 (32.9)	

Table Notes: See #1365 Jensen et al same study protocol used in United States and Canada; [a] Use of medications to relieve women of heavy menstrual bleeding (sex steroids, NSAIDS, tranexamic acid) was not allowed during study period; [b] Some women presented with multiple symptoms. [c] Complete response to treatment defined as composite of following components: no bleeding episodes lasting more than 7 days, no more than 4 bleeding episodes overall, no bleeding episodes with blood loss volume ≥80 ml, no more than one bleeding episode increase from baseline, no more than 24 days of bleeding overall and no increase from baseline in total number of bleeding days. In addition patients recruited because of presence of prolonged bleeding were required to demonstrate a decrease of at least 2 days in maximum duration of a bleeding cycle. Patients recruited because of heavy bleeding, the blood loss volume had to <80 ml and had to represent a decrease of at least 50% relative to average blood loss volume per episode during the study recruitment phase; [d] Change from 90 day run-in phase to 90-day efficacy phase; [e] Detail on criteria not achieved in partial or non-responders presented in Table 2 of manuscript (pg. 2702).

AUB KQ1 Evidence Table (Reference ID #1103)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Fraser et al., 1991 **Country:** Australia **Enrollment period:** NR **Intervention setting:** NR **Funding:** Parke-Davis Company Sydney, Australia **Author industry relationship disclosures:** NR **Study Design:** RCT (cross-over) **Blinding:** None	**Intervention[a]:** Mefenamic acid, 500 mg every 6-8 hours from first sign of menses until 24 hours after usual duration of heavy bleeding for a maximum of 5 days; Naproxen, 500 mg at first onset of menses followed by 250 mg every 6-8 hours until 24 hours after usual duration of heavy bleeding for a maximum of 5 days **Comparator:** Mefenamic acid, 500 mg every 6-8 hours from first sign of menses until 24 hours after usual duration of heavy bleeding for a maximum of 5 days; Low dose combined oral contraceptive (ethinyl estradiol 30 µg and levonorgestrel 150 µg) daily for 21 out of 28 days **Groups[b]:** **G1:** Cycles 1 and 2: no treatment Cycles 3 and 4: mefenamic acid or naproxen Cycles 5 and 6: no treatment Cycles 7 and 8: mefenamic acid or naproxen **G2:** Cycles 1 and 2: no treatment Cycles 3 and 4: mefenamic	**Inclusion criteria:** • Menorrhagia Regular periods Ovulating No hormonal therapy in the previous 3 months **Exclusion criteria:** Menorrhagia due to pelvic causes Menorrhagia due to systemic causes **N at enrollment:** **G1:** 15 **G2:** 15 **N at followup:** **G1:** 14 **G2:** 12 **Age:** NR **BMI:** NR **Parity:** NR **Race/ethnicity:** NR	**Bleeding:** MBL measured by alkaline hematin method in cycles 1 and 2, mean ml ± SD: **G1:** 131.1 ± 80.8 **G2:** 101.0 ± 52.5	**Bleeding:** MBL measured by alkaline hematin method during 2 mefenamic acid treatment cycles, mean ml ± SD: **G1:** 105.1 ± 88.6 **G2:** 62.9 ± 27.7 MBL % change from baseline during 2 mefenamic acid treatment cycles: **G1:** -20 **G2:** -38 **G1 vs. BL:** p=0.198 **G2 vs. BL:** p=0.002 MBL during 2 no treatment cycles 5 and 6, mean ml ± SD: **G1:** 131.9 ± 71.6 **G2:** 90.9 ± 61.3 MBL during 2 treatment cycles (G1: naproxen; G2: COC), mean ml ± SD: **Gb:** 115.6 ± 113.0 **Gc:** 57.8 ± 34.8 MBL % change from baseline during 2 treatment cycles (G1: naproxen; G2: COC): **Gb:** -12 **Gc:** -43 **Gb vs. BL:** p=0.079 **Gc vs. BL:** p<0.001	**Overall quality:** Poor **Risk of bias:** Randomization: Unclear Allocation concealment: Unclear Selective reporting: Low Blinding patients/personnel: High Blinding outcome assessment: High Incomplete outcome reporting: High Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
	acid or combined monophasic oral contraceptive Cycles 5 and 6: no treatment Cycles 7 and 8: mefenamic acid or combined monophasic oral contraceptive **Ga:** Mefenamic acid **Gb:** Naproxen **Gc:** Combined oral contraceptive **Followup:** 8 cycles			MBL reduction during 2 treatment cycles with mefenamic acid compared to 2 treatment cycles with naproxen and COC: **Gb vs. Ga:** p=0.129 **Gc vs. Ga:** p=0.079 Clinically significant[c] reduction in MBL during 2 mefenamic acid treatment cycles, n (%): **G1:** 8/14 (57) **G2:** 10/12 (83) Clinically significant[c] reduction in MBL during 2 treatment cycles, n (%): **Gb:** 9/14 (64) **Gc:** 9/12 (75) **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				Additional interventions: NR	

Table Notes: [a] A third group, not included in this review, received mefenamic acid and danazol (n=15); [b] The order of treatment within each group was randomized; [c] Objective reduction of 20% between the mean of first two cycles and mean of each 2 treatment cycles.

AUB KQ1 Evidence Table (Reference ID #1304, #1255)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Fraser et al., 1981 Fraser et al., 1984[a] **Country:** Australia **Enrollment period:** NR **Intervention setting:** NR **Funding:** Park-Davis and Co Australian National Health and Medical Research council **Author industry relationship disclosures:** NR **Study Design:** RCT (crossover) **Blinding:** Patients, clinicians	**Intervention:** Mefenamic acid 500mg, 3 times/day, onset to end of menses for 2 cycles followed by placebo for 2 cycles **Comparator:** Placebo for two cycles followed by mefenamic acid for 2 cycles **Groups:** **G1:** Mefenamic acid first then placebo **G2:** Placebo first then mefenamic acid **Ga:** Mefenamic acid **Gb:** Placebo **Followup:** 4 cycles	**Inclusion criteria:** Menorrhagia **Exclusion criteria:** See inclusion criteria **N at enrollment[a]:** **G1+G2:** 85 **N at followup:** **G1:** 38 **G2:** 31 **Age years, mean ± SD:** **G1+G2**: 33 ± 6.9 **BMI:** NR **Parity:** NR **Race/ethnicity:** NR	**Bleeding:** Menorrhagia duration, mean years ± SD: **G1+G2:** 11.2 ± 9.4 Dysmenorrhea duration, mean years ± SD: **G1+G2:** 11.6 ± 8.5 Bleeding days per cycle, mean ± SD: **G1+G2:** 3.3 ± 1.8 Pain, days per cycle, mean ± SD: **G1:** 3.1 ± 1.9 **G2:** 3.1 ± 1.7	**Bleeding:** MBL measured by alkaline hematin method, mean ml (SE): All patients (n=69): **Ga:** 48.1 (4.4) **Gb:** 66.9 (4.7) **Ga vs. Gb:** p<0.001 True menorrhagia (n=30): **Ga:** 77.2 (8.7) **Gb:** 110 (5.9) **Ga vs. Gb:** p<0.001 MBL <80 ml (n=39): **Ga:** 36.9 (3.4) **Gb:** 45.8 (2.6) **Ga vs. Gb:** p<0.025 MBL <35 ml (n=14): **Ga:** 31.6 (7.9) **Gb:** 24.7 (1.4) **Ga vs. Gb:** p=NS MBL measured by alkaline hematin method, mean ml (SE): **G1a:** 55.2 (4.9) **G1b:** 69.4 (5.5) **G2a:** 63.7 (4.7) **G2b:** 39.8 (4.2) **G1a vs. G1b:** p<0.05 **G2a vs. G2b:** p<0.001 **G1a vs. G2a:** p<0.02 **G1b vs. G2b:** p<0.4 Bleeding days per cycle, mean (SE): **Ga:** 4.9 (0.14) **Gb:** 5.3 (0.14) **Ga vs. Gb:** p<0.003 **Pain:**	**Overall quality:** Fair **Risk of bias:** Randomization: Unclear Allocation concealment: Unclear Selective reporting: Low Blinding patients/personnel: Low Blinding outcome assessment: Low Incomplete outcome reporting: High/Low Other: **Low**

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				Abdominal pain, days per cycle, mean (SE): **Ga:** 1.5 (0.13) **Gb:** 2.1 (0.15) **Ga vs. Gb:** p<0.001 Headache, days per cycle, mean (SE): **Ga:** 0.8 (0.14) **Gb:** 1.6 (0.16) **Ga vs. Gb:** p<0.001 Nausea, days per cycle, mean (SE): **Ga:** 0.6 (0.09) **Gb:** 0.7 (0.10) **Ga vs. Gb:** p=NS Diarrhea, days per cycle, mean (SE): **Ga:** 0.22 (0.06) **Gb:** 0.45 (0.09) **Ga vs. Gb:** p<0.008 Depression, days per cycle, mean ± SD: **Ga:** 0.8 (0.15) **Gb:** 1.1 (0.14) **Ga vs. Gb:** p=NS Breast symptoms, days per cycle, mean (SE): **Ga:** 0.9 (0.13) **Gb:** 1.1 (0.18) **Ga vs. Gb:** p=NS **Quality of life:** NR **Patient satisfaction:** NR	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				Fertility: NR **Time to conception:** NR **Additional interventions:** NR	

Table Notes: [a] Intrauterine device (n=6), fibroids (n=2), and Von Willebrand's disease (n=1); [b] Comparison of patients' subjective assessment of menstrual blood loss (60/69 87%) provided perception data accurate enough for analysis.

AUB KQ1 Evidence Table (Reference ID #1767)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Freeman et al., 2011 **Country:** United States **Enrollment period:** December 2006 to May 2008 **Intervention setting:** 63 participating study sites **Funding:** Ferring Pharmaceuticals, Inc **Author industry relationship disclosures:** 5/6 **Study Design:** RCT **Blinding:** Patients, investigators	**Intervention:** 3.9 g/day tranexamic acid (1.3 g 3 times daily) for up to 5 consecutive days **Comparator:** 1.95 g/day tranexamic acid (0.65 g 3 times a day) for up to 5 consecutive days Placebo **Groups:** **G1:** Tranexamic acid (3.9 g) **G2:** Tranexamic acid (1.95 g) **G3:** Placebo **Followup:** 3 cycles	**Inclusion criteria:** Aged 18-49 Average MBL during two pretreatment cycles ≥80 No abnormal findings at cervical cytology screening **Exclusion criteria:** History or presence of clinically significant disease History of bilateral oophorectomy or hysterectomy Pregnant, breastfeeding or planning pregnancy during the study Women with fibroids requiring surgical management **N at enrollment:** **G1:** 118 **G2:** 117 **G3:** 69 **N at followup:** **G1:** 112 **G2:** 115 **G3:** 67 **Age, mean years (range):** **G1:** 39.2 (20-50) **G2:** 40.2 (20-49) **G3:** 38.9 (19-48)	**Bleeding:** MBL measured by alkaline hematin method, mean mL/cycle: **G1:** 169.0 **G2:** 178.0 **G3:** 153.6 Duration, mean years ± SD: **G1:** 11.9 ± 8.9 **G2:** 12.1 ± 9.4 **G3:** 10.0 ± 8.4	**Bleeding:** MBL mean reduction from baseline, mL/cycle: **G1:** 65.3 **G2:** 46.5 **G3:** 3.0 **G1 vs. BL:** p<0.0001 **G2 vs. BL:** p<0.0001 **G3 vs. BL:** p=NS **G1 vs. G3:** p<0.0001 **G2 vs. G3:** p<0.0001 MBL % reduction from baseline: **G1:** 38.6 **G2:** 26.1 **G3:** 1.9 **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR	**Overall quality:** Fair **Risk of bias:** Randomization: Unclear Allocation concealment: Unclear Selective reporting: Low Blinding patients/personnel: Low Blinding outcome assessment: Unclear Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		BMI: NR **Parity:** NR **Race/ethnicity, n (%):** White: **G1:** 77 (67.0) **G2:** 76 (66.1) **G3:** 43 (64.2) Black: **G1:** 34 (29.6) **G2:** 31 (27.0) **G3:** 22 (32.8) Asian: **G1:** 0 **G2:** 3 (2.6) **G3:** 0 Native American: **G1:** 1 (0.9) **G2:** 0 **G3:** 0 Pacific Islander: **G1:** 0 **G2:** 1 (0.9) **G3:** 0 Other: **G1:** 3 (2.6) **G2:** 4 (3.5) **G3:** 2 (3.0)		**Adverse Events, n (%):** At least 1 adverse event: **G1:** 97 (84.4) **G2:** 104 (90.4) **G3:** 56 (83.6) Viral upper respiratory infection: **G1:** 8 (7.0) **G2:** 12 (10.4) **G3:** 3 (4.5) Fatigue: **G1:** 4 (3.5) **G2:** 13 (11.3) **G3:** 3 (4.5) Musculoskeletal pain: **G1:** 6 (5.2) **G2:** 10 (8.7) **G3:** 2 (3.0) Arthralgia: **G1:** 5 (4.4) **G2:** 7 (6.1) **G3:** 1 (1.5) Myalgia: **G1:** 6 (5.2) **G2:** 5 (4.4) **G3:** 0 Nasal congestion: **G1:** 3 (2.6) **G2:** 8 (7.0) **G3:** 0 Sinusitis: **G1:** 3 (2.6) **G2:** 7 (6.1) **G3:** 1 (1.5) Multiple allergies: **G1:** 4 (3.5) **G2:** 6 (5.2) **G3:** 0 Throat irritation: **G1:** 0 **G2:** 7 (6.1)	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				G3: 2 (3.0) Anemia: **G1:** 1 (0.9) **G2:** 6 (5.2) **G3:** 1 (1.5) Nausea: **G1:** 1 (0.9) **G2:** 1 (0.9) **G3:** 1 (1.5) Diarrhea/upper abdominal pain: **G1:** 0 **G2:** 1 (0.9) **G3:** 0 Lenticular opacity: **G1:** 1 (0.9) **G2:** 0 **G3:** 0 Blurred vision: **G1:** 1 (0.9) **G2:** 0 **G3:** 1 (1.5) Withdrawal from study for AEs not treatment related[a]: **G1:** 1 (0.9) **G2:** 3 (2.6) **G3:** 1 (1.5) Serious AE's not considered related to treatment[b]: **G1:** 1 (0.9) **G2:** 1 (0.9) **G3:** 0	

Table Notes:[a] mild myalgia (1 subject in G1); moderate anemia, moderate menorrhagia, severe anemia (1 subject each in G2) moderate headache (1 subject in G3); [b]1 subject in G1 experienced severe dyspepsia, gastritis, and chest pain and 1 subject in G2 experienced severe ovarian torsion on day 56 of study

AUB KQ1 Evidence Table (Reference ID #1114)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Grover et al., 1990 **Country:** India **Enrollment period:** January 1987 to October 1989 **Intervention setting:** Hospital **Funding:** NR **Author industry relationship disclosures:** NR **Study Design:** RCT **Blinding:** Patients, clinicians	**Intervention:** Mefenamic acid 500 mg 8 hourly from first day of cycle for 5 days or cessation of menses **Comparator:** Placebo tablets 3 times per day from first day of menses for 5 days **Groups:** **G1:** Mefenamic acid **G2:** Placebo **Followup:** 3 cycles	**Inclusion criteria:** Aged 19-50 years Cyclical menorrhagia defined subjectively Normal cervical cytology and secretory endometrium **Exclusion criteria:** History of drug sensitivity, thyroid, hepatic or renal disease **N at enrollment:** **G1:** 40 **G2:** 40 **N at followup:** **G1:** 40 **G2:** 40 **Age, mean years ± SD:** **G1:** 35.8 ± 7.5 **G2:** 35 ± 6.4 **BMI:** NR **Parity 2-4, %:** **G1+G2:** 80 **Race/ethnicity:** NR **Contraception,[a] laparo-scopic or post partum tubal ligation, %:** **G1:** 43 **G2:** 42	**Bleeding:** Menorrhagia duration, mean months ± SD: **G1:** 36 ± 2.5 **G2:** 32 ± 2.4 Bleeding days per cycle, mean ± SD: **G1:** 9.7 ± 3.1 **G2:** 8.8 ± 3.5 Amount of bleeding (measured subjectively by pads changed per day), mean ± SD: **G1:** 15.2 ± 3.1 **G2:** 14.7± 3.1	**Bleeding:** Relief of menorrhagia, %: **G1:** 86 **G2:** 20 **G1 vs. G2:** p<0.001 Bleeding days per cycle, mean ± SD: **G1:** 4.1 ± 0.6[c] **G2:** NR Amount of bleeding (measured subjectively by pads changed per day), mean ± SD: **G1:** 6.5 ± 0.02 **G2:** NR **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions:** Hysterectomy, n (%): **G1:** 2/40 (5)	**Overall quality:** Poor **Risk of bias:** Randomization: Unclear Allocation concealment: Unclear Selective reporting: Unclear Blinding patients/personnel: Unclear Blinding outcome assessment: Unclear Incomplete outcome reporting: Unclear Other: High

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		No previous treatment, %: **G1+G2:** 73 **Previous hormonal therapy,[b] %:** **G1+G2:** 27		**G2:** NR **Adverse events:** Gastritis, n (%): **G1:** 1 (2.5) **G2:** 0	

Table Notes: [a] No study patient was using an intrauterine device or hormonal contraception; [b] Combination pills or medroxyprogesterone acetate tablets 10 mg daily; [c] Authors state this is significant reduction from before treatment.

AUB KQ1 Evidence Table (Reference ID #1190)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Hall et al., 1987 **Country:** United Kingdom **Enrollment period:** NR **Intervention setting:** Outpatient clinics **Funding:** NR **Author industry relationship disclosures:** NR **Study Design:** RCT (crossover) **Blinding:** Patients, clinicians	**Intervention:** Naproxen loading dose 550 mg followed by 275 mg every 6 hours for 5 days **Comparator:** Mefenamic acid 500 mg every 8 hours **Groups:** **G1:** Naproxen in phase 1 and mefenamic acid in phase 2 **G2:** Mefenamic acid in phase 1 and naproxen sodium in phase 2 **Ga:** Naproxen **Gb:** Mefenamic acid **Followup:** 6 cycles	**Inclusion criteria:** • Aged 18 years through menopause Dysfunctional uterine bleeding MBL of >80ml confirmed in 2 initial control cycles **Exclusion criteria:** Pelvic inflammation Uterine fibroids Local disease Gross cyclic irregularities Taking NSAIDs, steroids Drug sensitivity Disorder requiring medical care Poor clinic attendance **N at enrollment[a]:** **G1:** 19 **G2:** 19 **N at follow-up:** **G1:** 17 **G2:** 16 **Age, mean years ± SD:** **G1:** 40.5 ± 3.6 **G2:** 38.1 ± 4.7 **BMI:** NR **Parity:** NR **Race/ethnicity:** NR	**Bleeding** MBL measured using the alkaline hematin method, median ml (range): **G1:** 118.5 (68, 186) **G2:** 129.3 (58, 369) **G1 vs. G2:** p=0.92 Bleeding days per cycle, mean ± SD: **G1:** 8.0 ± 2.8 **G2:** 6.6 ± 1.5 Hemoglobin, mean g/dl ± SD: **G1:** 13.0 ± 1.0 **G2:** 12.1 ± 1.70 **G1 vs. G2:** p=0.06 Serum iron, mean µmol/l ± SD: **G1:** 14.3 ± 5.96 **G2:** 11.8 ± 7.95 Tampons used, mean: **G1:** 31 **G2:** 32	**Bleeding** MBL measured using the alkaline hematin method (with slight modification to accommodate bulky material at phase 1), median ml (range): **G1:** 67.0 (15, 151) **G2:** 68.0 (22, 381) **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.001 **G1 vs. G2:** p=0.84 MBL at treatment phase 2, **G1**: 64.5 (22-135) **G2**: 67.3 (18-357) **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.001 **G1 vs. G2:** p=0.69 Bleeding days per cycle, mean, p value: **G1a:** 6.4 **G1b:** 5.9 **G2a:** 5.9 **G2b:** 6.0 **G1a vs. BL:** p=0.01 **G1b vs. BL:** p=0.01 **G2a vs. BL:** p=0.004 **G2b vs. BL:** p=0.03 Tampons used, mean: **G1a:** 23 **G1b:** 23 **G2a:** 25 **G2b:** 25 **G1a vs. BL:** p=0.003 **G1b vs. BL:** p=0.005 **G2a vs. BL:** p=0.003 **G2b vs. BL:** p=0.017	**Overall quality:** Fair **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Low Blinding patients/personnel: Low Blinding outcome assessment: Low Incomplete outcome reporting: High Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		Menorrhagia duration, mean number of months ± SD: **G1:** 55.8 ± 53.0 **G2:** 45.0 ± 41.4		**Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR **Adverse events, n:** Any side effects: **Ga:** 18 **Gb:** 15 Gastrointestinal[b]: **Ga:** 13 **Gb:** 6 Central nervous system symptoms[c]: **Ga:** 5 **Gb:** 6 Other[d]: **Ga:** NR **Gb:** NR	

Table Notes: [a] 50 patients at baseline, 9 withdrew before treatment, 1 withdrew in first treatment phase, 5 had <80 cc mbl, so 35 analyzed; [b] Included nausea, diarrhea, abdominal discomfort and anorexia; [c] Complaints of light headedness, dizziness, tiredness and headache; [d] A small number of patients in each treatment group noted weight increase, limb pain, pelvic discomfort, and post menstrual discharge.

AUB KQ1 Evidence Table (Reference ID #789)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Irvine et al., 1998 **Country:** United Kingdom **Enrollment period:** NR **Intervention setting:** Clinic **Funding:** NR **Author industry relationship disclosures:** NR **Study Design:** RCT **Blinding:** None	**Intervention:** Levonorgestrel-releasing intrauterine system inserted within the first seven days of menses **Comparator:** Norethisterone, 5 mg three times daily from cycle day 5 to 26 for three cycles **Groups:** **G1:** LNG-IUS **G2:** Norethisterone **Followup:** 3 months	**Inclusion criteria:** • Aged 18 to 45 years • Parous • Good general health with a regular menstrual cycle • Normal pelvic examination with a sound measurement of the uterus of <10 cm • Negative cervical cytology • Measured menstrual blood loss >80 ml **Exclusion criteria:** Treated with steroid hormones or anticoagulants during the previous three months • Used injectable hormones for contraception during the previous 12 months **N at enrollment:** **G1:** 22 **G2:** 22 **N at followup:** **G1:** 20 **G2:** 16 **Age, median years (range):** **G1**: 38.5 (31, 45) **G2**: 39 (30, 45)	**Bleeding:** MBL measured using alkaline haematin method, median ml (range): **G1:** 105 (82, 780) **G2:** 120 (82, 336) Hemoglobin, median g/dL (range): **G1:** 12.8 (11.7, 13.8) **G2:** 13.1 (11.1, 15.5) Serum ferritin, median ng/l (range): **G1:** 19 (4, 49) **G2:** 14 (<1, 53) Reported intermenstrual bleeding, n (%): **G1:** 11/22 (50) **G2:** 8/22 (36) Mood swings, n (%): **G1:** 19/22 (86) **G2:** 20/22 (91) Breast tenderness, n (%): **G1:** 19/22 (86) **G2:** 16/22 (73) Periods interfered with daily life, n (%): **G1:** 20/22 (91) **G2:** 18/22 (82)	**Bleeding:** MBL measured using alkaline haematin method, median ml (range): Cycle 1: **G1:** 16 (0, 62) **G2:** 46 (0, 213) Cycle 3: **G1:** 6 (0, 284) **G2:** 20 (4, 137) **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.001 MBL measured using alkaline haematin method, median reduction ml (range): Cycle 1: **G1:** 92 (63, 718) **G2:** 75 (-96, 225) Cycle 3: **G1:** 104 (-108, 73) **G2:** 94 (56, 209) **G1 vs. G2:** p=0.56 Hemoglobin/serum ferritin: **G1:** NR **G2:** NR **G1 vs. BL:** p=NS **G2 vs. BL:** p=NS Reported intermenstrual bleeding, n (%) **G1:** 10/19 (53) **G2:** 2/12 (17) Mood swings at 3 months, n (%): **G1:** 12/19 (63) **G2:** 7/12 (58)	**Overall quality:** Fair **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Unclear Blinding patients/personnel: Unclear Blinding outcome assessment: High Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		Height, median cm (range): **G1:** 158.5 (152, 170) **G2:** 159.5 (147, 178) **Weight, median kg (range):** **G1:** 69.9 (52.1, 116.0) **G2:** 71.4 (46.4, 96.6) **Parity, median (range):** **G1:** 2 (1, 5) **G2:** 2 (1, 5) **Race/ethnicity:** NR		**G1 vs. BL:** p=0.038 **G2 vs. BL:** p=0.038 **G1 vs. G2:** p=NS Breast tenderness at 3 months, n (%): **G1:** 14/19 (74) **G2:** 2/12 (17) **G1 vs. BL:** p=0.0003 **G2 vs. BL:** p=0.0003 **G1 vs. G2**: p=0.0008 Periods interfered with daily life at 3 months, n (%): **G1:** 6/19 (32) **G2:** 2/12 (17) **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.001 **G1 vs. G2**: p=NR Well or very well satisfied with treatment, n (%): **G1:** 14/22 (64) **G2:** 8/18 (44) Moderately or poorly satisfied with treatment, n (%): **G1:** 8/22 (36) **G2:** 10/18 (56) Continuation with the treatment, n (%): **G1:** 17/22 (77) **G2:** 4/18 (22) **Adverse events, n:** Withdrawal from study: **G1:** 2 **G2:** 6 Unacceptable drug related side effects:	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				G1: 1 **G2:** 2 Perceived treatment failure: **G1:** 0 **G2:** 2 Prolonged amenorrhea: **G1:** 0 **G2:** 1 LNG-IUS expulsion: **G1:** 1 **G2:** NA Default from final visit: **G1:** 0 **G2:** 1 Serious adverse events: **G1:** 0 **G2:** 0	

AUB KQ1 Evidence Table (Reference ID #1365[a])

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Jensen et al., 2011 **Country:** United States, Canada **Enrollment period:** December 2005 to May 2008 **Intervention setting:** 47 centers **Funding:** Bayer HealthCare Pharmaceuticals **Author industry relationship disclosures:** 5/5 **Study Design:** RCT **Blinding:** Patients, clinicians	**Intervention:** Estradiol valerate 3 mg on days 1–2; estradiol valerate 2 mg/dienogest 2 mg on days 3–7; estradiol valerate 2 mg/dienogest 3 mg on days 8–24; estradiol valerate 1 mg on days 25–26; placebo on days 27–28. **Comparator:** Placebo **Groups:** **G1:** Estradiol valerate/dienogest **G2:** Placebo **Followup:** 30 days	**Inclusion criteria:** • Aged 18 or older • Heavy menstrual bleeding (at least two bleeding episodes with a measured volume of ≥ 80 ml), prolonged menstrual bleeding (at least two bleeding episodes each lasting ≥ 8 days), frequent bleeding (> 5 bleeding episodes with a min of 20 bleeding days overall) or combination of any above criteria confirmed by use of electronic diaries and hemoglobin extraction from sanitary products • Women > 40 years had to have follicle-stimulating hormone level <40 miu/mL • Normal endometrial biopsy or mild simple endometrial hyperplasia 6 months before study entry • Willing to use a barrier method of contraception and to use (and collect) all sanitary protection items (pads and tampons) **Exclusion criteria:** Abnormal transvaginal	**Bleeding:** MBL measured by the alkaline hematin method, mean ml ± SD: **G1:** 518 ± 382 **G2:** 618 ± 432 Bleeding and spotting days, 90-day run-in phase, mean ± SD: **G1:** 25.1 ± 10.5 **G2:** 24.7 ± 9.7 Bleeding only days, 90-day run-in phase, mean ± SD: **G1:** 18.6 ± 7.5 **G2:** 17.9 ± 6.5 Spotting only days, 90-day run-in phase, mean ± SD: **G1:** 6.5 ± 6.0 **G2:** 6.8 ± 6.2 Bleeding episodes, 90-day run-in phase, mean ± SD: **G1:** 3.5 ± 0.8 **G2:** 3.5 ± 0.8 Sanitary protection items, 90-day run-in phase, mean ± SD: **G1:** 90 ± 42 **G2:** 96 ± 45 Hemoglobin, mean g/dl ± SD: **G1:** 12.2 ± 1.3 **G2:** 12.0 ± 1.4 Hematocrit, mean % ± SD: **G1:** 37.3 ± 3.6 **G2:** 37.0 ± 3.8	**Bleeding:** MBL measured by the alkaline hematin method, mean ml ± SD: **G1:** 196 ± 267 **G2:** 444 ± 306 MBL measured by the alkaline hematin method, mean change[e] ml ± SD: **G1:** -353 ± 309 **G2:** -130 ± 338 **G1 vs. G2:** p<0.001 Reduction in MBL volume, mean % (median %): **G1:** 64.2 (70.6) **G2:** 7.8 (18.7) **G1 vs. G2:** p<0.001 ≥20% reduction in MBL,%: **G1:** 91 **G2:** 51 ≥50% reduction in MBL,%: **G1:** 80 **G2:** 17 ≥80% reduction in MBL,%: **G1:** 45 **G2:** 5 Increase in MBL volume during treatment, %: **G1:** 5 **G2:** 20 MBL <80 ml for each episode, n (%): **G1:** 51/91 (56)	**Overall quality:** Good **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Unclear Blinding patients/personnel: Low Blinding outcome assessment: Low Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		ultrasonogram defined as the presence of uterine pathology, (e.g., fibroids or polyps whose size or location would be associated with heavy menstrual bleeding) Clinically significant abnormal values for any laboratory examination undergone in the 2 months before the study Endometrial ablation or dilatation and curettage Organic pathology including von Willebrand disease, chronic endometritis, adenomyosis, endometriosis, endometrial polyps, significant leiomyomas, or uterine malignancy Use of agents intended for the treatment of symptoms of abnormal uterine bleeding (e.g., tranexamic acid, nonsteroidal anti-inflammatory drugs, and sex steroids) BMI >32 kg/m^2 Smoking more than 10 cigarettes per day (in women older than 35	Ferritin, mean ng/ml ± SD: **G1:** 23.2 ± 35.1 **G2:** 21.2 ± 18.6	**G2:** 16/60 (26.7) Bleeding and spotting days, 90-day efficacy phase, mean ± SD: **G1:** 23.5 ± 13.1 **G2:** 22.9 ± 10.2 Bleeding and spotting days, mean change[e] ± SD: **G1:** -1.1 ± 14.0 **G2:** -2.3 ± 6.7 Bleeding only days, 90-day efficacy phase, mean ± SD: **G1:** 15.3 ± 9.6 **G2:** 16.0 ± 6.1 Bleeding only days, mean change[e] ± SD: **G1:** -2.8 ± 10.8 **G2:** -2.2 ± 4.6 **G1 vs. G2:** p=0.024 Spotting only days, 90-day efficacy phase, mean ± SD: **G1:** 8.2 ± 8.4 **G2:** 6.9 ± 6.7 Spotting only days, mean change[e] ± SD: **G1:** +1.7 ± 8.2 **G2:** -0.2 ± 4.9 Bleeding episodes, 90-day efficacy phase, mean ± SD: **G1:** 3.0 ± 1.2 **G2:** 3.2 ± 0.7 Bleeding episodes, mean change[e] ± SD:	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		years) Contraindications for the use of COCs **N at enrollment:** **G1:** 120 **G2:** 70 **N at followup:** **G1:** 84 **G2:** 51 **Age, mean years ± SD:** **G1:** 36.9 ± 7.5 **G2:** 37.0 ± 6.7 **BMI, mean kg/m^2 ± SD:** **G1:** 26.3 ± 3.6 **G2:** 25.8 ± 3.6 **Weight, mean kg ± SD:** **G1:** 71.3 ± 11.1 **G2:** 69.5 ± 11.8 **Parity:** NR **Race/ethnicity, n (%):** White: **G1:** 71(59.2) **G2:** 46(65.7) Black: **G1:** 38(31.7) **G2:**14(20.0) Hispanic: **G1:** 8(6.7) **G2:** 6(8.6) **Bleeding symptoms,[bc] n (%):** Prolonged bleeding:		**G1:** -0.5 ± 1.5 **G2:** -0.30 ± 0.9 **G1 vs. G2**: p=0.080 Sanitary protection items, 90-day efficacy phase, mean ± SD: **G1:** 51 ± 49 **G2:** 69 ± 29 Sanitary protection items, mean change[e] ± SD: **G1:** -44 ± 41 **G2:** -21 ± 43 **G1 vs. G2:** p<0.001 Hemoglobin, adjusted change from baseline, mean g/dl: **G1:** +0.6 **G2:** +0.1 **G1 vs. G2:** p=0.0004 Hematocrit, adjusted change from baseline, %: **G1:** +1.4 **G2:** -0.05 **G1 vs. G2:** p=0.001 Ferritin, adjusted change from baseline, mean ng/ml: **G1:** +2.9 **G2:** -0.4 **G1 vs. G2:** p=0.011 Patient reported improvement in bleeding symptoms, %: **G1:** 81.2 **G2:** 38.3 **G1 vs. G2:** p<0.001 Responder status[c] (ITT), n	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		G1: 26 (21.7) **G2:** 12 (17.1) Frequent bleeding: **G1:** 4 (3.3) **G2:** 2 (2.9) Heavy bleeding: **G1:** 91 (75.8) **G2:** 60 (85.7)		(%): Complete: **G1:** 35 (29.2) **G2:** 2 (2.9) **G1 vs. G2:** p<0.001 Partial or non-responder[d]: **G1:** 45 (37.5) **G2:** 46 (65.7) Missing data: **G1:** 40 (33.3) **G2:** 22 (31.4) Complete response rate (evaluable participants excluding missing data), n (%): **G1:** 35/80 (43.8) **G2:** 2/48 (4.2) **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR **Adverse events:**	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				Any adverse event, n (%): **G1:** 80/119 (67.2) **G2:** 36/66 (54.5) Discontinued treatment due to adverse events, n (%): **G1:** 11 (9.2) **G2:** 4 (6.1) Serious adverse event,[f] n: **G1:** 1 **G2:** 1 Adverse event, n (%): Acne: **G1:** 6 (5.0) **G2:** 0 Anemia: **G1:** 2 (1.7) **G2:** 4 (6.1) Anxiety: **G1:** 1 (0.8) **G2:** 3 (4.5) Arthralgia: **G1:** 0 **G2:** 3 (4.5) Back pain: **G1:** 3 (2.5) **G2:** 3 (4.5) Breast pain: **G1:** 5 (4.2) **G2:** 0 Breast tenderness: **G1:** 4 (3.4) **G2:** 1 (1.5) Bronchitis: **G1:** 3 (2.5) **G2:** 2 (3.0) Cervical dysplasia: **G1:** 3 (2.5) **G2:** 2 (3.0)	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				Chest pain: **G1:** 1 (0.8) **G2:** 2 (3.0) Depression: **G1:** 3 (2.5) **G2:** 1 (1.5) Diarrhea: **G1:** 3 (2.5) **G2:** 2 (3.0) Dizziness: **G1:** 0 **G2:** 2 (3.0) Dysmenorrhea: **G1:** 3 (2.5) **G2:** 2 (3.0) Dyspepsia: **G1:** 3 (2.5) **G2:** 0 Fatigue: **G1:** 4 (3.4) **G2:** 3 (4.5) Gastroenteritis: **G1:** 3 (2.5) **G2:** 0 Headache: **G1:** 5 (4.2) **G2:** 9 (13.6) Hypertension: **G1:** 2 (1.7) **G2:** 2 (3.0) Hypoesthesia: **G1:** 1 (0.8) **G2:** 2 (3.0) Influenza: **G1:** 3 (2.5) **G2:** 0 Insomnia: **G1:** 1 (0.8) **G2:** 2 (3.0) Metrorrhagia: **G1:** 6 (5.0)	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				G2: 0 Migraine: **G1:** 3 (2.5) **G2:** 0 Nasopharyngitis: **G1:** 9 (7.6) **G2:** 6 (9.1) Nausea: **G1:** 6 (5.0) **G2:** 5 (7.6) Sinusitis: **G1:** 4 (3.4) **G2:** 1 (1.5) Tension headache: **G1:** 4 (3.4) **G2:** 0 Upper respiratory tract infection: **G1:** 4 (3.4) **G2:** 1 (1.5) Vaginal infection: **G1:** 3 (2.5) **G2:** 0 Vaginitis bacterial: **G1:** 6 (5.0) **G2:** 4 (6.1) Vomiting: **G1:** 2 (1.7) **G2:** 2 (3.0) Vulvovaginal mycotic infection: **G1:** 4 (3.4) **G2:** 3 (4.5) Weight increase: **G1:** 7 (5.9) **G2:** 0	

Table Notes: [a] See #1349 Fraser et al; same study protocol used in Australia and Europe; [b] Some participants presented with multiple symptoms; [c] Complete response to treatment defined as composite of following components: no bleeding episodes lasting more than 7 days, no more than 4 bleeding episodes overall, no bleeding episodes with blood loss volume ≥80 ml, no more than one bleeding episode increase from baseline, no more than 24 days of bleeding overall and no increase from baseline in total number of bleeding days. In addition patients recruited because of presence of prolonged bleeding were required to demonstrate a decrease of at least 2 days in maximum duration of a bleeding cycle. Patients recruited because of heavy bleeding, the blood loss volume for each episode had to <80 ml and had to represent a decrease of at least 50% from the average of the qualifying bleeding episodes (ie episodes with blood loss volume ≥ 80 mL during the run-in phase); [d] Detail on criteria not achieved in partial or non-responders presented in Table

2 of manuscript (pg. 781); [e] Change from 90-day run-in to 90-day efficacy phase* compared with change from baseline with placebo; [f] Serious treatment emergent adverse events in treatment group a myocardial infarction and in placebo group hospitalization for a suicide attempt.

AUB KQ1 Evidence Table (Reference ID #32)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality and Risk of Bias
Author: Kaunitz et al., 2010 **Country**: United States, Canada, Brazil **Enrollment period**: July 2006 to June 2008 **Intervention setting**: 55 centers **Funding**: Bayer Schering Pharma AG **Author industry relationship disclosures**: 4/6 **Study Design**: RCT **Blinding**: None	**Intervention:** Levonorgestrel-releasing intrauterine system (LNG-IUS) placed within 7 days of onset of menstruation (in case of initial placement failure, only one attempt at replacement could be made) **Comparator:** Oral medroxyprogesterone 10 mg one daily for 10 days each cycle starting on cycle day 16 **Groups:** **G1:** LNG-IUS **G2:** Medroxyprogesterone **Followup:** Cycle 3 and cycle 6; 6 months	**Inclusion criteria:** • Aged ≥18 years • Parous • Idiopathic heavy MBL (≥80 ml per cycle) confirmed in at least two screening menstrual cycles before randomization Desiring intrauterine contraception and willing to use barrier contraception if required **Exclusion criteria:** Changes in menstrual regularity, hot flushes, sleeping disorders or changes in mood within 3 months preceding study Breastfeeding Congenital or acquired uterine abnormality including fibroids if they distorted the uterine cavity or cervical canal History of organic causes of AUB (e.g., endometriosis, adenomyosis, endometrial polyps)[a] Use of LNG-IUS or copper IUD during 30 days before the study History of vascular or coagulation disorders Concomitant use of medication or presence of underlying	**Bleeding:** MBL measured using the alkaline hematin method, median ml (range): **G1:** 148.0 (68.3, 431.4) **G2:** 154.2 (63.4, 456.0) Cycle length, mean days ± SD: **G1:** 27.2 ± 3.4 **G2:** 27.3 ± 2.3	**Bleeding:** MBL measured using the alkaline hematin method at mid-study, median ml (range): **G1:** 30.3 (0, 317.5) **G2:** 136.2 (0, 404.8) MBL at end of study, median ml (range): **G1:** 7.1 (0, 1435.6) **G2:** 121.5 (0, 437.7) MBL change from baseline, mean ml (95% CI): Mid-study: **G1:** -108.3 (-125.4, -91.2) **G2:** -21.2 (-38.1, -4.3) End of study: **G1:** -114.7 (-144.2, -85.1) **G2:** -39.0 (-68.2, -9.8) MBL change from baseline, median ml (range): Mid-Study: **G1:** -115.1 (-405.8, 54.4) **G2:** -3.2 (-270.9, 146.7) **G1 vs. G2:** p<0.001 End of study: **G1:** -128.8 (-393.6, 1242.2) **G2:** -17.8 (-271.5, 78.6) **G1 vs. G2:** p<0.001	**Overall quality:** Fair **Risk of Bias:** Randomization: Low Allocation concealment: Low Selective reporting: Low Blinding patients/personnel: High Blinding outcome assessment: Unclear Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality and Risk of Bias
		disease/condition known to affect metabolism or pharmacokinetics of study medication BMI >35 kg/m^2 **N at enrollment:** **G1:** 82 **G2:** 83 **N at followup:** **G1:** 73 **G2:** 72 **Age, mean years ± SD:** **G1:** 38.3 ± 5.2 **G2:** 39.3 ± 5.4 **BMI, mean kg/m^2 ± SD:** **G1:** 27.2 ± 3.9 **G2:** 27.4 ± 4.6 **Parous, %:** **G1+G2:** 100 **Births, mean number (range):** **G1:** 2.5 (1, 5) **G2:** 2.6 (1, 7) **Race/ethnicity, n (%):** White: **G1:** 56 (68.3) **G2:** 62 (74.7) Black: **G1:** 17 (20.7) **G2:** 13 (15.7) Hispanic: **G1:** 6 (7.3) **G2:** 6 (7.2) Asian:		MBL % change from baseline, mean ± SD: Mid-study: **G1:** -61.7 ± 41.8 **G2:** -11.1 ± 42.5 **G1 vs. G2:** p<0.001 End of study: **G1:** -70.8 ± 88.3 **G2:** -21.5 ± 35.8 **G1 vs. G2:** p<0.001 MBL % change from baseline, median (range): Mid-study: **G1:** -83.2 (-100.0, 44.3) **G2:** -2.2 (-100.0, 231.5) End of study: **G1:** -95.4 (-100.0, 642.3) **G2:** -13.1 (-100.0, 51.1) Proportion in which treatment was successful,[b] n (%) **G1:** 67/79 (84.8) **G2:** 18/81 (22.2) **G1 vs. G2:** p<0.001 **Quality of life:** NR **Pain:** NR **Sexual function:** NR	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality and Risk of Bias
		G1: 2 (2.4) **G2:** 1 (1.2) Other: **G1:** 1 (1.2) **G2:** 1 (1.2)		**Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR **Adverse events:** Deaths or serious adverse events, n: **G1:** 0 **G2:** 0 Withdrawal from study, n: **G1:** 4 **G2:** 2 Expulsion of LNG-IUS,[c] n: Full: **G1:** 2 **G1:** NA Partial: **G1:** 2 **G2:** NA Drug related adverse events, n (%): **G1+G2:** 69 (42.6) Headache: **G1:** 13 (16.3) **G2:** 9 (11.0) Ovarian cyst:	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality and Risk of Bias
				G1: 10 (12.5) **G2:** 2 (2.4) Vaginitis, bacterial: **G1:** 9 (11.3) **G2:** 3 (3.7) Urinary tract infection: **G1:** 6 (7.5) **G2:** 3 (3.7) Acne: **G1:** 5 (6.3) **G2:** 5 (6.1) Hypertension: **G1:** 5 (6.3) **G2:** 1 (1.2) Sinusitis: **G1:** 5 (6.3) **G2:** 3 (3.7) Upper respiratory tract infection: **G1:** 5 (6.3) **G2:** 1 (1.2) Breast tenderness: **G1:** 4 (5.0) **G2:** 3 (3.7) Fatigue: **G1:** 4 (5.0) **G2:** 2 (2.4) Pelvic pain: **G1:** 4 (5.0) **G2:** 2 92.4) Increased weight: **G1:** 4 (5.0) **G2:** 5 (6.1) Lower abdominal pain: **G1:** 3 (3.8) **G2:** 5 (6.1)	

Table Notes: [a] Three or more subserous or intramural fibroids with a total volume of less than 5 cm^3 were acceptable; [b] Treatment success defined as MBL <80 ml at end of study and 50% or greater reduction in MBL from baseline. [c] One woman experienced heavy bleeding after expulsion of the system.

AUB KQ1 Evidence Table (Reference ID #493)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Kennedy et al., 2002 **Country:** England (UK) **Enrollment period:** October 1996 to February 1998 **Intervention setting:** 6 hospitals **Funding:** Grant from UK National Health Service **Author industry relationship disclosures:** None **Study Design:** RCT **Blinding:** None (not possible)	**Intervention:** Interview group received booklet and videotape at their home 6 weeks before consultation and had an interview immediately before consultation Information group received booklet and videotape at their home 6 weeks before consultation **Comparator:** Standard practice control group received no intervention **Groups:** **G1:** Interview plus information **G2:** Information only **G3:** Control **Followup:** 2 years (questionnaires sent at 6,12, and 24 months post consultation)	**Inclusion criteria:** • Referred from primary to secondary care with uncomplicated menorrhagia if referral related to new episode of menorrhagia • Deemed nonurgent by their consultant **Exclusion criteria:** See inclusion criteria **N at enrollment:** (Randomized) **G1:** 300 **G2:** 296 **G3:** 298 (Returned baseline questionnaire) **G1:** 298 **G2:** 293 **G3:** 294 **N at followup:** **G1:** 215 **G2:** 206 **G3:** 204 **Age, mean years ± SD:** **G1:** 41 ± 6.9 **G2:** 40 ± 7.2 **G3:** 40 ± 7.0 **Age leaving full-time education, n (%):** ≤16: **G1:** 171 (57.0) **G2:** 171 (57.8) **G3:** 172 (57.7)	Knowledge of available treatments,[a] mean ± SD: **G1:** 65 ± 23.2 **G2:** 66 ± 21.2 **G3:** 68 ± 21.0 Menorrhagia severity,[b] mean ± SD: **G1:** 48 ± 14.8 **G2:** 47 ± 13.8 **G3:** 47 ± 14.8 Treatment preference held, n (%): **G1:** 139 (47.6) **G2:** 117 (41.1) **G3:** 130 (45.6)	Clinicians perception of consultation length “longer than usual”, %: **G1:** 28.5 **G2:** 16.9 **G3:** 18.9 Health status measured by SF-36 score,[c] role physical dimension: **G1:** NR **G2:** NR **G3:** NR **G1 vs. G2:** p=NS **G1 vs. G3:** p=0.04 **G2 vs. G3:** p=NS **Bleeding:** NR **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** Self reported opportunity to take part in treatment decision making, OR (95% CI): **G1 vs. G3:** 1.49 (1.11, 2.01) **G2 vs. G3:** 1.24 (0.91, 1.69) **G1 vs. G2:** p=NS **G1 vs. G3:** p=0.008 **G2 vs. G3:** p=NS	**Overall quality:** Poor **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Low Blinding patients/personnel: High Blinding outcome assessment: High Incomplete outcome reporting: High Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		17-18: **G1:** 69 (23.0) **G2:** 74 (25.0) **G3:** 73 (24.5) ≥ 19: **G1:** 50 (16.7) **G2:** 44 (14.9) **G3:** 44 (14.8) Unknown: **G1:** 10 (3.3) **G2:** 7 (2.4) **G3:** 9 (3.0) **Menorrhagia duration, n (%):** Less than 1 year: **G1:** 63 (21.2) **G2:** 73 (25.0) **G3:** 64 (21.8) 1-2 years: **G1:** 58 (19.5) **G2:** 64 (21.9) **G3:** 67 (22.9) 2-3 years: **G1:** 48 (16.2) **G2:** 40 (13.7) **G3:** 45 (15.4) More than 3 years: **G1:** 128 (43.1) **G2:** 115 (39.4) **G3:** 117 (39.9) **Previous treatment, n (%):** Hormonal drugs: **G1:** 84 (32.7) **G2:** 91 (36.1) **G3:** 99 (40.1) Non-hormonal drugs: **G1:** 96 (37.4) **G2:** 108 (42.9) **G3:** 103 (41.7)		Self reported rating of overall results of treatment, OR (95% CI): **G1 vs. G3:** 1.44 (1.03, 2.01) **G2 vs. G3**: 1.16 (0.85, 1.60) **G1 vs. G2:** p=NS **G1 vs. G3:** p=0.03 **G2 vs. G3**: p=NS **Fertility:** NR **Time to conception:** NR **Additional interventions (during 2 year followup):** Underwent at least one treatment,[d] n (%): **G1:** 212 (83.8) **G2:** 204 (78.9) **G3:** 196 (80.3) Hysterectomy, n (%): **G1:** 81 (38.2) **G2:** 98 (48.0) **G3:** 94 (48.0) OR (95% CI): **G1 vs. G3:** 0.60 (0.38, 0.96) **G2 vs. G3:** 1.16 (0.73, 1.85) **G1 vs. G2:** p=NS **G1 vs. G3:** p=0.04 **G2 vs. G3:** p=NS Endometrial destruction, n (%): **G1:** 25 (11.8) **G2:** 15 (7.4)	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		Oral contraceptive pill: **G1:** 61 (23.7) **G2:** 55 (21.8) **G3:** 58 (23.5) Dilation and curettage: **G1:** 55 (21.4) **G2:** 64 (25.4) **G3:** 55 (22.3) **Ever had any surgery, n (%):** **G1:** 248 (84.9) **G2:** 236 (83.1) **G3:** 238 (83.2)	**G3:** 16 (8.2) OR (95% CI): **G1 vs. G3:** 0.88 (0.33, 2.30) **G2 vs. G3:** 0.51 (0.18, 1.42) Drug therapy, n (%): **G1:** 145 (68.4) **G2:** 138 (67.6) **G3:** 119 (60.7) OR (95% CI): **G1 vs. G3:** 1.48 (0.93, 2.36) **G2 vs. G3:** 1.40 (0.87, 2.25) Other treatment, n (%): **G1:** 43 (20.3) **G2:** 39 (19.1) **G3:** 36 (18.4) OR (95% CI): **G1 vs. G3:** 1.14 (0.68, 1.89) **G2 vs. G3:** 0.99 (0.59, 1.67) Underwent or waiting for hysterectomy, n (%): **G1:** 82 (38.7) **G2:** 101 (49.3) **G3:** 101 (51.5) OR (95% CI): **G1 vs. G3:** 0.53 (0.35, 0.83) **G2 vs. G3:** 1.03 (0.67, 1.60)	

Table Notes: [a] Scored 0-2 for knowledge of 7 treatment options, then transformed to a 0-100 scale; [b] Assessed using a menorrhagia outcome scale; [c] Adjusted mean health status scores only displayed graphically in figure 2 (pg. 2704), no other dimensions showed a significant difference between groups; [d] Women may have received more than 1 treatment.

AUB KQ1 Evidence Table (Reference ID #267)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Kriplani et al., 2006 **Country:** India **Enrollment period:** November 2002 to November 2004 **Intervention setting:** Hospital/clinic single site **Funding:** Indian Council of Medical Research **Author industry relationship disclosures:** NR **Study Design:** RCT **Blinding:** None	**Intervention:** Tranexamic acid 500 mg four times daily for five days starting on cycle day one **Comparator:** Medroxyprogesterone acetate 10 mg twice daily from cycle day 5 to 25 for 3 months **Groups:** **G1:** Tranexamic acid **G2:** Medroxyprogesterone **Followup:** 6 months	**Inclusion criteria:** • Menorrhagia (PBLAC score >100) **Exclusion criteria:** Fibroids, adenomyosis, endometriosis, atypia on endometrial histopathology Thyroid disease Hormone therapy in previous 3 months **N at enrollment:** **G1:** 50 **G2:** 50 **N at followup:** **G1:** 49 **G2:** 45 Duration of menorrhagia, mean months: **G1:** 26 **G2:** 24 **Age, mean years ± SD (range):** **G1:** 36.43 ± 8.25 (15, 50) **G2:** 36.67 ± 7.54 (19, 49) **Parity, mean (range)** **G1:** 3.06 ± 1.38 (0, 8) **G2:** 2.84 ± 1.26 (0, 6) **Courses completed:** 1: **G1:** 48 **G2:** 45 2:	**Bleeding:** MBL, measured by PBLAC score, mean: **G1:** 356.94 **G2:** 370.24 Duration of bleeding, mean days: **G1:** 7.08 **G2:** 8.36 Cycle length, mean days: **G1:** 26.9 **G2:** 26.6 Hemoglobin, mean g%: **G1:** 10.71 **G2:** 10.83 Endometrial thickness, mean mm: **G1:** 7.40 **G2:** 7.46	**Bleeding:** MBL, measured by PBLAC score, mean: Month one: **G1:** 149.17 **G2:** 167.93 Month two: **G1:** 138.92 **G2:** 179.51 Month three: **G1**: 141.64 **G2**: 156.67 Month six: **G1**: 239.6 **G2**: 242.6 PBLAC score, % change: Month one: **G1:** -58.2 **G2:** -54.6 Month two: **G1:** -61.0 **G2:** -51.5 Month three: **G1:** -60.3 **G2:** -57.7 Month six: **G1:** -32.0 **G2:** -35.3 PBLAC score < 100 at month three, n (%): **G1:** 19 (38.8) **G2:** 15 (33.3) Hemoglobin at month three, mean g%: **G1:** 11.2 **G2:** 11.4	**Overall quality:** Poor **Risk of bias:** Randomization: Low Allocation concealment: Unclear Selective reporting: Unclear Blinding patients/personnel: High Blinding outcome assessment: High Incomplete outcome reporting: High Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		G1: 48 **G2:** 41 3: **G1:** 47 **G2:** 33 **Race/ethnicity:** NR		**G1 vs. BL:** p=0.003 **G2 vs. BL:** p=0.019 Lack of response to treatment, n (%): **G1:** 3 (6.1) **G2:** 13 (28.9) **G1 vs. G2:** p=0.003 **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** Liked treatment well or very well, %: **G1:** 78.7 **G2:** 69.7 Elected to continue treatment, %: **G1:** 63.8 **G2:** 48.5 **Fertility:** NR **Time to conception:** NR **Additional interventions:** Hysterectomy during 6 month study period, n (%): **G1:** 2 (4)	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				G2: 8 (17.8) **G1 vs. G2:** p=0.002 Hysterectomy at one year after stopping study, n: **G1:** 8/30 **G2:** 1/25	

Table Notes: No additional medication allowed during study period. Iron supplementation was given only when hemoglobin level was < 8 g%.

AUB KQ1 Evidence Table (Reference ID #189)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Kucuk et al., 2008 **Country:** Turkey **Enrollment period:** August 2005 to May 2006 **Intervention setting:** Single center **Funding:** NR **Author industry relationship disclosures:** NR **Study Design:** RCT **Blinding:** None	**Intervention:** LNG-IUS(Mirena) on cycle day 2 or 3 **Comparators:** Single shot of depot medroxyprogesterone acetate on first day of cycle Medroxyprogesterone acetate 5 mg tablet every day starting on first day of cycle **Groups:** **G1:** LNG-IUS **G2:** Depot medroxy-progesterone **G3:** Medroxyproges-terone **Followup:** 6 months	**Inclusion criteria:** • Menorrhagia[a] Perimenopausal[b] Smoker **Exclusion criteria:** Organic pathology Occasional smokers Irregular bleeding but non-menorrhagic **N at enrollment:** **G1:** 44 **G2:** 44 **G3:** 44 **N at followup:** **G1:** 44 **G2:** 44 **G3:** 44 **Age, mean years ± SD:** **G1:** 42.8 ± 1.1 **G2:** 43.1 ± 1.6 **G3:** 42.6 ± 1.9 **BMI, mean kg/m^2 ± SD:** **G1:** 29.1 ± 3.3 **G2:** 27.1 ± 4.4 **G3:** 26.4 ± 3.9 **Parity, mean ± SD:** **G1:** 1.9 ± 0.3 **G2:** 1.8 ± 0.4 **G3:** 1.9 ± 0.6 **Smoker, %:** **G1:** 100 **G2:** 100 **G3**: 100	**Bleeding:** MBL, measured by modified PBLAC score, mean ± SD: **G1:** 287 ± 57 **G2:** 284 ± 50 **G3:** 230 ± 36 Menstruation duration, mean days ± SD: **G1:** 9 ± 2 **G2:** 9 ± 2 **G3:** 9 ± 1 Hemoglobin, mean g/dl ± SD: **G1**: 10.1 ± 0.4 **G2**: 9.7 ± 0.4 **G3**: 10.2 ± 0.7	**Bleeding:** MBL at 6 months, measured by modified PBLAC score, mean ± SD: **G1:** 77 ± 41 **G2:** 146 ± 21 **G3:** 154 ± 30 **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.001 **G3 vs. BL:** p<0.001 **G1 vs. G2:** p<0.01 **G1 vs. G3:** p<0.01 **G2 vs. G3:** p=NS Treatment success, n (%): **G1:** 38 (86) **G2:** 33 (75) **G3:** 30 (68) Menstruation duration, mean days ± SD: **G1:** 5 ± 2 **G2:** 7 ± 1 **G3:** 5 ± 1 **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.001 **G3 vs. BL:** p<0.001 **G1 vs. G2:** p=NS **G1 vs. G3:** p=NS **G2 vs. G3:** p=NS Hemoglobin, mean g/dl ± SD, p-value: **G1:** 10.9 ± 0.4 **G2:** 10.2 ± 0.4 **G3:** 10.8 ± 0.7 **G1 vs. BL:** p<0.01 **G2 vs. BL:** p<0.01	**Overall quality:** Poor **Risk of bias:** Randomization: High Allocation concealment: High Selective reporting: Unclear Blinding patients/personnel: Unclear Blinding outcome assessment: Unclear Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		Race/ethnicity: NR		**G3 vs. BL:** p<0.01 **G1 vs. G2:** p<0.05 **G1 vs. G3:** p<0.05 **G2 vs. G3:** p=NS **Quality of life:** NR **Pain** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR **Adverse events, n (%):** Irregular bleeding: **G1:** 6 (13.6) **G2:** 9 (20.4) **G3:** 12 (27.2) Breast tenderness: **G1:** 6 (13.6) **G2:** 9 (20.4) **G3:** 12 (27.2) Willing to continue treatment: **G1:** 38 (86.3) **G2:** 25 (56.8) **G3:** 19 (43.1)	

Table Notes: [a] Diagnosis established after following diagnostic workup: hemogram, modified PBLAC, prothrombin time, activated prothrombin time, ALT, AST, hormonal profile including FSH, LH, estradiol, prolactin, B-HCG, sTSH, T3 T1, Pap smear, endometrial biopsy, transvaginal sonography and saline infusion sonography, and diagnostic office hysteroscopy when needed; [b] Women over age 40; [c] PBLAC score >185 considered unresponsive; PBLAC score <185 considered response.

AUB KQ1 Evidence Table (Reference ID #802)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Lahteenmaki et al., 1998 **Country:** Finland **Enrollment period:** November 1991 to December 1993 **Intervention setting:** 3 clinics **Funding:** Leiras Oy, Turku, Finland **Author industry relationship disclosures:** None **Study Design:** RCT **Blinding:** None	**Intervention:** Levonorgestrel-releasing intrauterine system inserted according to instructions **Comparator:** Existing medical treatment **Groups:** **G1:** LNG-IUS **G2:** Control (current medical treatment) **Followup:** **G1:** 12 months **G2:** 6 months	**Inclusion criteria:** • Women with spontaneous cycles scheduled to undergo hysterectomy for treatment of excessive uterine bleeding with or without dysmenorrhea **Exclusion criteria:** One fibroid >3 cm in diameter or more than 3 uterine fibroids as assessed by ultrasonography History or current malignancy or active liver disease Adnexal tumors or cysts Pelvic Inflammatory Disease within the previous 12 months **N at enrollment:** **G1:** 28 **G2:** 28 **N at followup:** **G1:** 27 **G2:** 26[a] **Age, mean years ± SD:** **G1:** 42.7 ± 3.4 **G2:** 41.7 ± 4.5 **BMI:** NR **Parity:** NR	**Menstrual disturbance:** General well being VAS, median (95% CI): **G1:** 90 (74, 94) **G2:** 87 (77, 92) **G1 vs. G2:** p=NS Work performance VAS, median (95% CI): **G1:** 79 (62, 89) **G2:** 75 (61, 80) **G1 vs. G2:** p=NS Physical activity VAS, median (95% CI): **G1:** 88 (64, 95) **G2:** 78 (64, 92) **G1 vs. G2:** p=NS Sex life VAS, median (95% CI): **G1:** 68 (49, 86) **G2:** 66 (52, 80) **G1 vs. G2:** p=NS Leisure time activity VAS, median (95% CI): **G1:** 76 (54, 86) **G2:** 74 (64, 85) **G1 vs. G2:** p=NS	**Bleeding:** Bleeding, median days per month:[b] Months 1 to 3: **G1:** NR **G2:** NR **G1 vs. G2:** p=NS Months 4 to 6: **G1:** NR **G2:** NR **G1 vs. G2:** p=NS Spotting, median days per month:[b] Months 1 to 3: **G1:** NR **G2:** NR **G1 vs. G2:** p=0.001 Months 4 to 6: **G1:** NR **G2:** NR **G1 vs. G2:** p=0.016 **Menstrual disturbance:** General well being VAS, median (95% CI): 6 months: **G1:** 24 (14, 40) **G2:** 79 (64, 87) **G1 vs. G2:** p<0.001 12 months: **G1:** 10 (4, 29) **G2:** NR Work performance VAS, median (95% CI): 6 months: **G1:** 20 (5, 35) **G2:** 76 (54, 87) **G1 vs. G2:** p<0.001	**Overall quality:** Poor **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Unclear Blinding patients/personnel: Unclear Blinding outcome assessment: High Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		Race/ethnicity: NR		12 months: **G1:** 6 (3, 11) **G2:** NR Physical activity VAS, median (95% CI): 6 months: **G1:** 27 (9, 38) **G2:** 78 (55, 88) **G1 vs. G2:** p<0.001 12 months: **G1:** 10 (3, 28) **G2:** NR Sex life VAS, median (95% CI): 6 months: **G1:** 36 (17, 49) **G2:** 66 (51, 85) **G1 vs. G2:** p=0.002 12 months: **G1:** 8 (3, 28) **G2:** NR Leisure time activity VAS, median (95% CI): 6 months: **G1:** 11 (5, 27) **G2:** 74 (54, 86) **G1 vs. G2:** p<0.001 12 months: **G1:** 6 (3, 29) **G2:** NR **Additional interventions:** Cancelled hysterectomy at 6 months, % (95% CI): **G1:** 64.3 (44.1, 81.4) **G2:** 14.3 (4.0, 32.7) **G1 vs. G2:** p<0.001	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				Underwent hysterectomy at 12 months, n (%): **G1:** 12 (57) **G2:** NR Switched to LNG-IUS at 6 months, n: **G1:** NA **G2:** 2/26 Continued with LNG-IUS at average followup of 3 years, n (%): **G1:** 13 (48) **G2:** NR **Adverse events, n:** Serious adverse events: **G1+G2:** 0	

Table Notes: [a] At 6 months, two women in G2 switched to LNG-IUS; [b] Values only displayed graphically in Figures 1 and 3 (pg. 1124).

AUB KQ1 Evidence Table (Reference ID #29)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Lukes et al., 2010 **Country:** United States **Enrollment period:** October 2006 to May 2008 **Intervention setting:** Outpatient clinic at 40 sites **Funding:** Xanodyne Pharmaceuticals and Ferring Pharmaceuticals **Author industry relationship disclosures:** 11/12 **Study Design:** RCT **Blinding:** Patients, investigators	**Intervention:** Tranexamic acid 1.3 g per dose (two 650 mg tablets) to start at onset of heavy bleeding, 3 times daily at least 6 hours apart for up to 5 days per cycle over 6 menstrual cycles (maximum dose 3.9 g) **Comparator:** Placebo **Groups:** **G1:** Tranexamic acid **G2:** Placebo **Followup:** 6 cycles	**Inclusion criteria:** • Aged 18 to 49 years • History of three or more consecutive days of heavy bleeding over at least 4 of last 6 menstrual periods During two-cycle pretreatment baseline phase, menstrual blood loss had to be at least 60 ml during first period and average at least 80 ml over both cycles Normal findings on pelvic exam No clinically important cervical cytology abnormalities or uterine pathologic findings by transvaginal ultrasonography[a] History of regularly occurring menstrual periods of no more than 10 days duration and cycle length of 21 to 35 days Normal color vision **Exclusion criteria:**[b] History or presence of significant medical problems (e.g., thromboembolic disease, coagulopathy, subarachnoid hemorrhage, endocrinopathy, or ocular disease	**Bleeding:** Duration of heavy menstrual bleeding, mean years ± SD: **G1:** 9.9 ± 9.3 **G2:** 10.1 ± 8.6 Uterine leiomyomas present at baseline, n (%): **G1:** 42 (36.5) **G2:** 26 (36.1) MBL measured by the alkaline hematin method,[c] mean ml ± SD: **G1:** 172.3 ± 95.6 **G2:** 153.0 ± 66.6 **G1 vs. G2:** p=0.11 Anemia, n (%): **G1:** 39/115 (33.9) **G2:** 13/72 (18.1)	**Bleeding:** MBL measured by the alkaline hematin method[c] reduction, mean ml (%): **G1:** 69.6 (40.4) **G2:** 12.6 (8.2) **G1 vs. G2:** p<0.001 MBL reduction ≥50 ml, % of cycles: **G1:** 56 **G2:** 19 **G1 vs G2:** p<0.001 MBL reduction ≥36 ml, % of cycles: **G1:** 69 **G2:** 29 **G1 vs. G2:** p<0.001 MBL <80 ml, cycles (%): **G1**: 181/426 (43) **G2**: 43/254 (17) **G1 vs. G2:** p<0.001 Women with ≥50% reduction in MBL from baseline, %: **G1:** 35 **G2:** 7 **G1 vs G2:** p<0.001 Hemoglobin level change from baseline, mean g/dl ± SD: **G1:** 0.02 ± 1.10 **G2:** 0.34 ± 0.66 **G1 vs. BL:** p=NS **G2 vs. BL:** p<0.001	**Overall quality:** Good **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Low Blinding patients/personnel: Low Blinding outcome assessment: Low Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		Severe anemia (hemoglobin < 8 g/dL) Pregnant or lactating History or presence of endometrial abnormalities or cervical carcinoma Anovulatory dysfunctional uterine bleeding, metrorrhagia, menometrorrhagia, or polymenorrhea Glaucoma, ocular hypertension, macular degeneration or retinopathies **N at enrollment:** **G1:** 123 **G2:** 73 **N at followup ITT:** **G1:** 115 **G2:** 72 **N completed study:** **G1:** 94 **G2:** 54 **Age, mean years ± SD:** **G1:** 38.7 ± 6.4 **G2:** 38.7 ± 6.8 **Race, n (%):** White: **G1:** 86 (73.5) **G2:** 51 (70.8) African American: **G1:** 23 (19.6) **G2:** 18 (25.0) Asian: **G1:** 1 (0.9)		Ferritin concentration change from baseline, mean ng/ml ± SD: **G1:** -1.21 ± 12.70 **G2:** -2.68 ± 16.15 **G1 vs. BL:** p=NS **G2 vs. BL:** p=NS Treatment compliance, % tablets taken: **G1**+**G2:** 96.3 (n=188) Treatment days per cycle, mean: **G1:** 3.4 **G2:** 3.3 **Quality of life:** MIQ limitation score, changes in least-squares mean from baseline ± SD: Social or leisure activities: **G1:** 0.85 ± 0.13 **G2:** 0.44 ± 0.12 **G1 vs. G2:** p<0.001 Physical activity: **G1:** 0.87 ± 0.13 **G2:** 0.40 ± 0.14 **G1 vs. G2:** p< 0.001 **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		G2: 1 91.4) Other: **G1:** 7 (6.0) **G2:** 2 (2.8) **Years of alcohol use, n (%):** Less than 1: **G1:** 1 (1.9) **G2:** 1 (2.9) 1-5: **G1:** 9 (17.0) **G2:** 7 (20.0) More than 5: **G1:** 43 (81.1) **G2:** 27 (77.1) **Years of tobacco use, n (%):** Less than 1: **G1:** 1 (2.4) **G2:** 1 (3.7) 1-5: **G1:** 9 (22.0) **G2:** 5 (18.5) More than 5: **G1:** 31 (75.6) **G2:** 21 (77.8)		**Time to conception:** NR **Additional interventions:** NR **Adverse events:** Serious adverse events (all judged unrelated to study treatment), n: **G1:** 5 **G2:** 1 Ocular-related adverse events judged possibly or probably study related, n: **G1:** 2 **G2:** 5 Frequently reported[f] treatment emergent adverse events, n (%): Menstrual discomfort/cramps **G1:** 72 (61.5) **G2:** 36 (50.0) Headache: **G1:** 65 (55.6) **G2:** 36 (50.0) Back pain: **G1:** 28 (23.9) **G2:** 14 (19.4) Nausea: **G1:** 17 (14.5) **G2:** 11 (15.3) Anemia: **G1:** 12 (10.3) **G2:** 4 (5.6) Arthralgia:	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				G1: 11 (9.4) **G2:** 5 (6.9) Viral upper respiratory tract infection: **G1:** 9 (7.7) **G2:** 7 (9.7) Multiple allergies **G1:** 10 (8.5) **G2:** 5 (6.9) Abdominal discomfort: **G1:** 8 (6.8) **G2:** 6 (8.3) Cough: **G1:** 7 (6.0) **G2:** 5 (6.9) Insomnia: **G1:** 6 (5.1) **G2:** 6 (8.3) Fatigue: **G1:** 8 (6.8) **G2:** 3 (4.2) Muscle cramps: **G1:** 8 (6.8) **G2:** 3 (4.2) Dyspepsia: **G1:** 3 (2.6) **G2:** 8 (11.1) Migraine: **G1:** 7 (6.0) **G2:** 4 (5.6) Sinus headache: **G1:** 9 (7.7) **G2:** 2 (2.8)	

Table Notes: [a] Transvaginal ultrasonogram considered abnormal if endometrial thickness was > 12 mm or if the endometrial thickness was 5 to 12 mm and patient's clinical history suggested long-term unopposed estrogen exposure (≥ 1 year). If transvaginal ultrasonogram was considered abnormal, normal results on endometrial biopsy were required. Presence of leiomyomas was not considered an abnormal finding unless they were of sufficient number and size to warrant surgical management; [b] Participants were not allowed to use anticoagulants, aspirin, dong quai, aminocaproic acid, hydroxychloroquine during the study. Cyclooxygenase-2 inhibitors and NSAIDs were not allowed during menstrual periods, but were permitted during intermenstrual phase of the cycle. Use of acetaminophen, analgesic opioids, oral iron therapy, and vitamins were permitted throughout the study. Oral iron therapy prescribed at investigator's discretion for women with hemoglobin levels between 11 g/dL-12 g/dL at baseline. It was required for women with baseline hemoglobin < 11 g/dL and for women whose hemoglobin declined to < 11 g/dL during the study; [c] Prespecified three component primary efficacy endpoint for mean reduction in

MBL: 1) significantly greater than placebo group; 2) greater than 50 mL from baseline; and 3) greater reduction in MBL previously established to be perceived as meaningful (36 mL or higher); [d] 1 each of: tachycardia, acute bronchitis, hypoglycemia, posttraumatic stress disorder, and urticaria; [e] Deep vein thrombosis; [f] Events that occurred in more than 10 participants irrespective of causality.

AUB KQ1 Evidence Table (Reference ID #1381)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Najam et al., 2010 **Country:** India **Enrollment period:** October 2008 to September 2009 **Intervention setting:** Teaching hospital **Funding:** NR **Author industry relationship disclosures:** NR **Study Design:** RCT **Blinding:** Single blinded	**Intervention:** Tranexamic acid 500 mg thrice daily, from cycle day 1 to cycle day 5 **Comparator:** Combination tranexamic acid 500 mg and mefenamic acid 250 mg thrice daily from cycle day 1 to cycle day 5 for 3 cycles **Groups:** **G1:** Tranexamic acid **G2:** Tranexamic acid plus mefenamic acid **Followup:** 6 months	**Inclusion criteria:** Aged 12 to 45 years Endometrial thickness less than 5 mm using transvaginal sonography evaluation on cycle day 4, 5, or 6 for married women Normal Pap test, thyroid function test, renal function tests, liver function tests, coagulation profile Endometrium sampling for the secretory phase, only in cases of the perimenopausal age group **Exclusion criteria:** History of recent intrauterine device or hormonal therapy Anovulatory or irregular cycles Pregnancy, pelvic pathology, coagulation disturbances, polycystic ovarian disease Thyroid, liver or renal dysfunction **N at enrollment:** **G1**: 55 **G2:** 55 **N at followup:** **G1:** 55 **G2:** 55 **Age, mean years (range):** **G1:** 37 (13, 49) **G2:** 39 (12, 47) **BMI, mean kg/m^2:**	**Bleeding:** MBL measured by PBLAC,[a] score, mean (range): **G1:** 250 (221, 267) **G2:** 246 (213, 254) Hemoglobin, mean g/dl (range): **G1:** 9.5 (7.2, 11.8) **G2:** 8.6 (6.5, 10.2) No anemia (hemoglobin >11 gm %), n (%): **G1:** 2 (1.8) **G2:** 4 (3.6) Mild anemia (hemoglobin 10-11 gm %), n (%): **G1:** 13 (23.6) **G2:** 17 (30.9) Moderate anemia (hemoglobin 7-9.9 gm %), n (%): **G1:** 33 (60) **G2:** 27 (49) Severe anemia (hemoglobin 4-6.9 gm %), n (%): **G1:** 8 (7.2) **G2:** 6 (5.4)	**Bleeding:** MBL measured by PBLAC[a] score, mean: 1 month: **G1:** 185 **G2:** 155 6 months: **G1:** 125, p> 0.05 **G2:** 100, p< 0.01 **G1 vs. BL:** p=NS **G2 vs. BL:** p<0.01 Hemoglobin, mean g/dl: 1 month: **G1:** 10.2 **G2:** 10.6 **G1 vs. BL:** p=NS **G2 vs. BL:** p=0.04 3 months: **G1:** 11.4 **G2:** 11.8, **G1 vs. BL:** p=NS **G2 vs. BL:** p=0.02 6 months: **G1:** 12.0 **G2:** 12.3 **G1 vs. BL:** p=0.04 **G2 vs. BL:** p=0.016 **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR	**Overall quality:** Poor **Risk of bias:** Randomization: Low Allocation concealment: Unclear Selective reporting: Unclear Blinding patients/personnel: High Blinding outcome assessment: High Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		G1: 22 **G2:** 21 **Parity:** NR **Race/ethnicity:** NR Menorrhagia, n (%): **G1+G2:** 75 (68) Polymenorrhagia, n (%): **G1+G2:** 28 (25.4) Metrorrhagia, n (%): **G1+G2:** 7 (6.3) Symptom duration, median months (range): **G1:** 10.5 (4.5, 16) **G2:** 11.7 (3.6, 13.6)		**Fertility:** NR **Time to conception:** NR **Additional interventions:** NR **Adverse events, n (%):** Nausea and gastrointestinal disturbances: **G1:** 9 (16.4) **G2:** 8 (14.5) Leg cramps: **G1:** 7 (12.7) **G2:** 12 (21.8)	

Table Notes: [a] PBAC score of ≥100 indicates diagnosis of menorrhagia and signifies that MBL is more than 80 ml.

AUB KQ1 Evidence Table (Reference ID #935)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Preston et al., 1995 **Country:** United Kingdom **Enrollment period:** NR **Intervention setting:** Hospitals and clinics **Funding:** Pharmacia **Author industry relationship disclosures:** NR **Study Design:** RCT, double blind, placebo controlled **Blinding:** Patients, clinicians	**Intervention:** Tranexamic acid 1 gm, 4 times a day on days 1 to 4 and placebo on days 19 to 26 **Comparator:** Placebo on days 1 to 4 and norethisterone 5 mg twice per day on days 19 to 26 Cycle 1: Placebo Cycle 2: Placebo Cycle 3: Treatment Cycle 4: Treatment **Groups:** **G1:** Tranexamic acid **G2:** Norethisterone **Followup:** 4 months	**Inclusion criteria:** • Aged 18 or older • Cycle length 28 ± 7 days • No hormone therapy within previous 3 months • Not taking medication which might affect MBL • No contraindication to either drug • Normal renal function (serum creatinine <125 µmol/l) • Normal pelvic examination • Negative cervical cytology • Menorrhagia (average MBL over 2 cycles >80 ml per cycle) Regular cycle **Exclusion criteria:** See inclusion criteria **N at enrollment:** **G1:** 25 **G2:** 21 **N at followup:** **G1:** 25 **G2:** 21 **Age, mean years ± SD:** **G1:** 40.6 ± 4.7 **G2:** 39.3 ± 7.1 **BMI:**	**Bleeding:** MBL measured using the alkaline hematin method at cycles 1 and 2 combined,[a] mean ml ± SD: **G1:** 175 ± 84 **G2:** 173 ± 85 Hemoglobin,[b] mean g/dl ± SD: **G1:** 12.3 ± 1.2 **G2:** 12.0 ± 1.4 Serum ferritin,[b] mean µg/l ± SD: **G1:** 11.2 ± 11.4 **G2:** 8.9 ± 7.2 Transferrin,[b] mean g/dl ± SD: **G1:** 3.68 ± 0.42 **G2:** 3.64 ± 0.56	**Bleeding:** MBL measured using the alkaline hematin method at cycles 3 and 4 combined,[c] mean ml ± SD: **G1:** 97 ± 89 **G2:** 208 ± 135 **G1 vs. BL:** p<0.0001 **G2 vs. BL:** p=0.26 **G1 vs. G2:** p<0.0001 MBL estimated reduction from baseline, ml (95% CI): **G1:** 79 (62, 108) **G2:** -34 (-64, 2) **G1 vs. G2:** 113 (71, 155) MBL % change from baseline, mean (range): **G1:** -45 (-93, 23) **G2:** 20 (-62, 114) MBL < 80 ml per cycle, n: **G1:** 14/25 **G2:** 2/21 Hemoglobin, mean g/dl ± SD: **G1:** 12.9 ± 0.9 **G2:** 12.6 ± 1.6 Serum ferritin, mean µg/l ± SD: **G1:** 11.5 ± 6.0 **G2:** 10.3 ± 6.8	**Overall quality:** Fair **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Unclear Blinding patients/personnel: Low Blinding outcome assessment: Low Incomplete outcome reporting: High Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		NR **Weight, mean kg ± SD:** **G1:** 71.2 ± 14.9 **G2:** 63.5 ± 9.2 **G1 vs. G2:** p<0.048 **Parity, n (%):** 0: **G1:** 1 (4) **G2:** 1 (5) 1: **G1:** 2 (8) **G2:** 3 (14) 2: **G1:** 13 (52) **G2:** 10 (48) 3: **G1:** 9 (36) **G2:** 6 (29) 4: **G1:** 0 **G2:** 1 (5) **Race/ethnicity:** NR		Transferrin, mean g/dl ± SD: **G1:** 3.34 ± 0.34 **G2:** 4.74 ± 0.53 **Quality of life:** General health, n (%): Better: **G1:** 12 (50) **G2:** 6 (30) Same/worse: **G1:** 12 (50) **G2:** 14 (70) Amount of flooding and leakage, n (%): Better: **G1:** 20 (83) **G2:** 9 (45) Same/worse: **G1:** 4 (17) **G2:** 11 (55) **G1 vs. G2:** p=0.008 Limitation of social activities, n (%): Better: **G1:** 16 (67) **G2:** 9 (45) Same/worse: **G1:** 8 (33) **G2:** 11 (55) **Pain:** Abdominal pain, n (%): Better: **G1:** 9 (38) **G2:** 4 (20) Same/worse: **G1:** 15 (62) **G2:** 16 (80)	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				Sexual function, n (%): Better: **G1:** 11 (46) **G2:** 3 (15) Same/worse: **G1:** 13 (54) **G2:** 17 (85) **G1 vs. G2:** p=0.029 **Patient satisfaction:** Assessment of blood loss during treatment compared to placebo cycle, n (%): Better: **G1:** NR **G2:** NR Same/worse: **G1:** NR **G2:** NR **G1 vs. G2:** p=0.002[d] **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR **Adverse events:** Dysmenorrhea, %: **G1:** 80 **G2:** 85 Headache, %: **G1:** 32 **G2:** 48 Gastrointestinal	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				symptoms including diarrhea, nausea, vomiting, and dyspepsia, %: **G1:** 12 **G2:** 33 Weight gain, n: **G1:** 2 **G2:** 0	

Table Notes: [a] Data also given for cycles 1 and 2 separately; [b] Laboratory values are from the pre-placebo phase; [c] Data also given for cycles 3 and 4 separately; [d] Patients treated with tranexamic acid were significantly better than those treated with norethisterone.

AUB KQ1 Evidence Table (Reference ID #1441)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Protheroe et al., 2007 **Country:** United Kingdom **Enrollment period:** July 2003 to January 2005 **Intervention setting:** 19 general practices **Funding:** Grant from Medical Research Council **Author industry relationship disclosures:** None **Study Design:** RCT **Blinding:** NR	**Intervention:** Self-directed, interactive computerized decision aid (Clinical Guidance Tree) and patient information leaflet Treatment options included watchful waiting, nonhormonal drug treatments (mefenamic acid, tranexamic acid, NSAIDS and ethamsylate), hormonal medications (COC and progestogens), LNG-IUS (Mirena) and surgical options (transcervical endometrial resection, abdominal or vaginal hysterectomy) **Comparator:** Control: Patient information leaflet alone **Groups:** **G1**: Decision aid **G2**: Control **Followup:** 6 months	**Inclusion criteria:** • Aged 30-55 years • Menorrhagia and consulted their general practitioner in the previous week **Exclusion criteria:** • Heavy menstrual bleeding caused by physical pathology such as confirmed or provisional diagnosis of cancer, endometriosis, fibroids, polyps and cysts • Inability to understand English • Considered unsuitable by their general practitioner (including terminal illness, mental health problems) **N at enrollment:** **G1:** 74 **G2:** 72 **N at followup (%):** **G1:** 60 (81) **G2:** 56 (78) **Age years, mean ± SD:** **G1:** 41 ± 5.2 **G2:** 41 ± 5.4 **BMI:** NR **Parity:** NR **Race/ethnicity:** NR	Decisional Conflict Scale total score,[b] mean ± SD: **G1:** 51 ± 20.6 **G2:** 50 ± 19.4 Spielberger State-Trait Anxiety Inventory score,[c] mean ± SD: **G1:** 12.7 ± 4.2 **G2:** 13.4 ± 4.2 Menorrhagic Specific Utility Scale score,[b] mean ± SD: **G1:** 36.2 ± 19.6 **G2:** 39.9 ± 21.8 Knowledge (% of correct answers), mean ± SD: **G1:** 36.7 ± 18.8 **G2:** 36.5 ± 21.0 Baseline treatment preference, n (%): Had a treatment preference at baseline: **G1:** 47 (63) **G2:** 45 (62) Tablets: **G1:** 20 (27) **G2:** 22 (30.5) Surgery: **G1:** 22 (30) **G2:** 18 (25) Hormone intrauterine device: **G1:** 5 (6.5) **G2:** 5 (7) Unsure: **G1:** 27 (36.5)	Decisional Conflict Scale total score[b] at 2 weeks, mean ± SD: **G1:** 23.4 ± 14.3 (n=69) **G2:** 40.5 ± 18.3 (n=69) **G1 vs. G2:** p<0.001 Decisional Conflict Scale total score[b] at 2 weeks, adjusted difference (95% CI): **G1 vs. G2:** -16.6 (-21.5, -11.7) Spielberger State-Trait Anxiety Inventory score,[c] mean ± SD: 2 weeks: **G1:** 11.6 ± 3.7 (n=59) **G2:** 12.2 ± 3.7 (n=61) **G1 vs. G2:** p=0.16 6 months: **G1:** 11.2 ± 4.2 (n=47) **G2:** 13.3 ± 4.9 (n=52) **G1 vs. G2:** p=0.067 Spielberger State-Trait Anxiety Inventory score,[c] adjusted difference (95% CI): 2 weeks: **G1 vs. G2:** -1.0 (-2.4, 0.4) 6 months: **G1 vs. G2:** -1.8 (-3.7, 0.1) Menorrhagic Specific Utility Scale score, mean ± SD: **G1:** 59.3 ± 30.0 (n=60) **G2:** 50.9 ± 25.1 (n=56)	**Overall quality:** Poor **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Unclear Blinding patients/personnel: High Blinding outcome assessment: High Incomplete outcome reporting: Low Other: Unclear

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
			G2: 27 (37.5)	**G1 vs. G2:** p=0.033	
		Achieved higher education, n (%): **G1:** 17 (23) **G2:** 15 (21)		Menorrhagic Specific Utility Scale score, adjusted difference (95% CI): **G1 vs. G2:** 10.9 (0.9, 21.0)	
				Knowledge (% of correct answers), mean ± SD: **G1:** 59.7 ± 18.4 (n=54) **G2:** 48.8 ± 19.6 (n=54) **G1 vs. G2:** p=0.014	
				Knowledge (% of correct answers), adjusted difference (95% CI): **G1 vs. G2:** 9.3 (1.9, 16.6)	
				Bleeding: NR	
				Quality of life: NR	
				Pain: NR	
				Sexual function: NR	
				Patient satisfaction: NR	
				Fertility: NR	
				Time to conception: NR	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				Additional interventions,[a] n (%): Treatment at 6 months: **G1:** 40 (71) **G2:** 45 (80) **G1 vs. G2:** p=0.268 Treatment preference at two weeks: **G1:** 49 (88) **G2:** 38 (68) **G1 vs. G2:** p=0.011 Post intervention preference matches treatment received: **G1:** 23 (58) n=40 **G2:** 20 (44) n=45 **G1 vs. G2:** p=0.198 Hospital appointment: **G1:** 19 (34) **G2:** 21 (38) **G1 vs. G2:** p=0.659 Surgical treatment: **G1:** 7 (13) **G2:** 3 (5) **G1 vs. G2:** p=0.139 Mirena: **G1:** 13 (23) **G2:** 15 (27) **G1 vs. G2:** p=0.625 Medical treatment: **G1:** 20 (36) **G2:** 27 (48) **G1 vs. G2:** p=0.198	

Table Notes: [a] For G1 and G2 total n=56 in each group unless otherwise noted; [b] Scale 0-100; [c] Scale 6-24, where higher score indicates higher anxiety.

AUB KQ1 Evidence Table (Reference ID #341)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Reid and Virtanen-Kari, 2005 **Country:** United Kingdom **Enrollment period:** May 1996 to December 1998 **Intervention setting:** District general hospital **Funding:** Schering Oy **Author industry relationship disclosures:** 2/2 **Study Design:** RCT **Blinding:** None	**Intervention:** LNG-IUS, 52 mg levonorgestrel in cylinder initial release rate 20 µg per 24 hours **Comparator:** Oral mefenamic acid, 500 mg three times daily for first 4 days of cycle **Groups:** **G1:** LNG-IUS **G2:** Mefenamic acid **Followup:** 6 cycles	**Inclusion criteria:** • Aged 18 to 47 years Good general health with regular, ovulatory menstrual cycles of 21 to 35 days Idiopathic menorrhagia (MBL ≥80 mL) confirmed in one cycle within 4 month period preceding study **Exclusion criteria:** Undiagnosed abnormal bleeding Anovulatory Submucous fibroids or fibroids with total volume of >5 cm^3 defined by ultrasound scan Uterine size of >10 cm Abnormal cervical cytology Untreated hypertension Abnormal thyroid or liver function tests Asthma Intrauterine device Treated for menorrhagia or used hormonal contraceptives within previous 4 months **N at enrollment:** **G1:** 25 **G2:** 26 **N at followup (cycle 6):** **G1:** 21 **G2:** 21 **Age, mean years:** **G1:** 39.4	**Bleeding:** MBL, measured by modified alkaline hematin technique, median ml (range): **G1:** 122 (81, 375) **G2:** 121 (85, 389) Total menstrual fluid loss,[a] median mL (range): **G1:** 183 (103-527) **G2:** 211 (91-491) PBAC score, median (range): **G1:** 240 (91-545) **G2:** 233 (77-469)	**Bleeding:** MBL, measured by modified alkaline hematin technique, median ml (range): Cycle 3: **G1:** 12 (0, 240) **G2:** 94 (29, 219) **G1 vs. G2:** p<0.001 Cycle 6: **G1:** 5 (0, 45) **G2:** 100 (46, 168) **G1 vs. G2:** p< 0.001 Total menstrual fluid loss, median mL (range): Cycle 3: **G1:** 53 (0, 459) **G2:** 151 (57, 280) **G1 vs. G2:** p<0.001 Cycle 6: **G1:** 27 (0, 156) **G2:** 157 (76, 319) **G1 vs. G2:** p<0.001 PBAC score, median (range): Cycle 3: **G1:** 49 (0, 286) **G2:** 161 (77, 262) **G1 vs. G2:** p<0.001 Cycle 6: **G1:** 25 (0, 402) **G2:** 159 (50, 307) **G1 vs. G2:** p<0.001 **Quality of life:** NR **Sexual function:** NR	**Overall quality:** Poor **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Unclear Blinding patients/personnel: High Blinding outcome assessment: High Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		G2: 38.5 **BMI:** NR **Parity:** NR **Race/ethnicity:** NR		**Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR **Adverse events, n:** Abdominal pain: **G1:** 8/25 **G2:** 2/26 Headache: **G1:**10/25 **G2:** 10/25 Breast pain: **G1:** 6/25 **G2:** 2/26 Nausea: **G1:** 2/25 **G2:** 4/26 Diarrhea: **G1:** 1/25 **G2:** 4/25 Upper respiratory infection: **G1:** 5/25 **G2:** 5/26 LNG-IUS expulsion: **G1:** 4/25 **G2:** NA	

Table Notes: [a] Total menstrual fluid loss was determined by difference in weight between returned sanitary material and original weight. Correlations between change in total menstrual fluid loss and PBAC scores over the six cycles when all patients were analyzed together (r=0.88, p<0.0001). PBAC scores correlated with changes in MBL (r=0.53, p= 0.0007) and total menstrual fluid loss (r=0.58, p=0.0002).

AUB KQ1 Evidence Table (Reference ID #17)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Shaaban et al., 2011 **Country:** Egypt **Enrollment period:** May 2003 to March 2004 **Intervention setting:** Gynecology outpatient clinic, Assiut University **Funding:** Lab work funding provided by Assiut University; LNG-IUS donated by Bayer Schering Pharma AG; sanitary pads provided by Proctor and Gamble **Author industry relationship disclosures:** NR **Study Design:** RCT **Blinding:** None	**Intervention:** Levonorgestrel-releasing intrauterine system inserted per manufacturer's instructions **Comparator:** Low dose combined oral contraceptive (30 mcg of ethinyl estradiol/150 mcg levonorgestrel) **Groups:** **G1:** LNG-IUS **G2:** Combined oral contraceptive **Followup:** 12 months	**Inclusion criteria:** • Heavy menstrual bleeding (self described) • Requested contraception • 20 to 50 years old at initial assessment • Regular cycle • Living in nearby area **Exclusion criteria:** Pregnancy or history of ectopic pregnancy Puerperal sepsis Pelvic inflammatory disease Evidence of defective coagulation Ultrasound abnormalities including fibroid of any size History or evidence of malignancy or hyperplasia in the endometrial biopsy Incidental adnexal abnormality on ultrasound Contraindications to COC Previous endometrial ablation or resection Uninvestigated postcoital bleeding Untreated abnormal cervical cytology **N at enrollment:**	**Bleeding:** MBL measured by alkaline hematin method, mean ml ± SD: **G1:** 300.0 ± 150.1 **G2:** 274.3 ± 142.6 **G1 vs. G2:** p=0.383 PBLAC, mean score ± SD: **G1:** 306.7 ± 131.8 **G2:** 323.8 ± 97.3 **G1 vs. G2:** p=0.787 Hemoglobin, mean g/dl ± SD: **G1:** 10.2 ± 1.3 **G2:** 10.5 ± 1.2 **G1 vs. G2:** p=0.207 Ferritin, mean µg/dl ± SD: **G1:** 31.8 ± 108.3 **G2:** 88.8 ± 193.6 **G1 vs. G2:** p=0.057 Uterine weight, mean g ± SD: **G1:** 115.9 ± 38.6 **G2:** 128.7 ± 38.0 **G1 vs. G2:** p=0.080 HRQoL-4, health ≥ very good, n (%): **G1:** 3 (5.3) **G2:** 3 (5.3) Physically unhealthy days in past month, mean ± SD:	**Bleeding:** MBL measured by alkaline hematin method at 12 months,[a] mean ml ± SD: **G1:** 44.4 ± 34.9 **G2:** 118.2 ± 75.0 **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.001 **G1 vs. G2:** p<0.001 MBL reduction at 12 months, mean % ± SD: **G1:** 87.4 ± 11.3 **G2:** 35.0 ± 77.0 **G1 vs. G2:** p=0.013 PBLAC at 12 months, mean score[a] ± SD: **G1:** 31.6 ± 35.1 **G2:** 273.0 ± 238.4 **G1 vs. BL:** p<0.001 **G2 vs. BL:** p=0.129 **G1 vs. G2:** p<0.001 PBLAC score[a] reduction at 6 months, mean % ± SD: **G1:** 89.5 ± 11.7 **G2:** 41.6 ± 53.6 **G1 vs. G2:** p<0.001 PBLAC score reduction at 12 months, mean % ± SD: **G1:** 86.6 ± 17.0 **G2:** 2.5 ± 93.2 **G1 vs. G2:** p<0.001 Hemoglobin at 12	**Overall quality:** Poor **Risk of bias:** Randomization: Low Allocation concealment: High Selective reporting: Low Blinding patients/personnel: High Blinding outcome assessment: Unclear Incomplete outcome reporting: Low Other: High

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		G1: 56 **G2:** 56 **N (%) at followup:** **G1:** 48 (85.7) **G2:** 47 (83.9) **Age, mean years ± SD:** **G1:** 39.3 ± 6.7 **G2:** 38.7 ± 5.2 **Age at menarche, mean years ± SD:** **G1:** 11.6 ± 1.0 **G2:** 11.5 ± 1.4 **BMI, mean kg/m^2 ± SD:** **G1:** 29.6 ± 5.9 **G2:** 31.1 ± 5.7 **BMI >30 kg/m^2, n (%):** **G1:** 25 (48.1) **G2:** 32 (57.1) **Parity:** NR **Previous deliveries, median (IQR):** **G1:** 3 (1, 6.4) **G2:** 3 (2, 6) **Race/ethnicity:** NR	**G1:** 7.4 ± 2.7 **G2:** 7.5 ± 2.6 Mentally unhealthy days in past month, mean ± SD: **G1:** 5.9 ± 2.8 **G2:** 6.2 ± 3.1 Activity limitation (lost days) in past month, mean ± SD: **G1:** 6.8 ± 2.6 **G2:** 7.0 ± 2.7	months, mean g/dl ± SD: **G1:** 11.4 ± 1.0 **G2:** 10.1 ± 1.2 **G1 vs. BL:** p<0.001 **G2 vs. BL:** p=0.081 **G1 vs. G2:** p<0.001 Ferritin at 12 months, mean µg/dL ± SD: **G1:** 88.5 ± 101.6 **G2:** 54.3 ± 91.3 **G1 vs. BL:** p=0.005 **G2 vs. BL:** p=0.230 **G1 vs. G2:** p<0.001 Uterine weight at 12 months, mean g ± SD: **G1:** 98.2 ± 33.3 **G2:** 154.8 ± 54.0 **G1 vs. BL:** p<0.001 **G2 vs. BL:** p=0.004 **G1 vs. G2:** p<0.001 Total bleeding days per year,[a] mean ± SD: **G1:** 34.5 ± 12.0 **G2:** 65.1 ± 15.3 **G1 vs. G2:** p<0.001 Total spotting days per year,[a] mean ± SD: **G1:** 20.7 ± 8.9 **G2:** 18.0 ± 10.6 **G1 vs. G2:** p=0.273 **Quality of life:** HRQoL-4, health ≥ very good at 12 months, n (%): **G1:** 15 (26.8) **G2:** 13 (23.2)	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				G1 vs. BL: p<0.001 **G2 vs. BL:** p<0.001 **G1 vs. G2:** p=0.129 Physically unhealthy days in past month at 12 months, mean ± SD: **G1:** 3.7 ± 2.0 **G2:** 4.7 ± 2.7 **G1 vs. BL:** p<0.001 **G2 vs. BL:** p=0.034 **G1 vs. G2:** p=0.186 Mentally unhealthy days in past month at 12 months, mean ± SD: **G1:** 6.7 ± 3.1 **G2:** 4.4 ± 1.7 **G1 vs. BL:** p=0.954 **G2 vs. BL:** p=0.357 **G1 vs. G2:** p=0.003 Activity limitation (lost days) in past month at 12 months, mean ± SD: **G1:** 1.6 ± 2.4 **G2:** 6.7 ± 2.2 **G1 vs. BL:** p=0.003 **G2 vs. BL:** p=0.794 **G1 vs. G2:** p<0.001 **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:**	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				NR **Time to conception:** NR **Additional interventions:** NR **Adverse Events:** Treatment failure,[b] n (%): **G1:** 6 (11) **G2:** 18 (32) **G1 vs. G2:** HR=0.30 (95% CI: 0.14, 0.73), p=0.007 Treatment failure reasons, n: Removal for lost threads with persistent bleeding: **G1:** 1 **G2:** NR Expulsion: **G1:** 1 **G2:** NR Persistent bleeding: **G1:** 4 **G2:** NR	

Table Notes: [a] Patients with amenorrhea were considered to have a MBL of 0 mL, PBLAC score of 0 and no bleeding or spotting; [b] Treatment failure defined as initiation of an alternative medical treatment, need for surgery, confirmed expulsion, or removal of LNG-IUS.

AUB KQ1 Evidence Table (Reference ID #1180)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Tsang et al., 1987 **Country:** Canada **Enrollment period:** NR **Intervention setting:** NR **Funding:** Grants from Medical Research Council of Canada; Parke-Davis Canada, Inc,[a] Ottawa Civic Hospital fund and University Medical Research fund; Dept of Obstetrics and Gynecology, University of Ottawa **Author industry relationship disclosures:** NR **Study Design:** RCT (crossover) **Blinding:** Patients, investigators	**Intervention:** Mefenamic acid 500 mg at onset of menses followed by 250 mg every 6 hours for 3 to 5 days for cycles 2 and 3 followed by placebo for cycles 4 and 5. **Comparator:** Placebo for cycles 2 and 3 followed by mefenamic acid for cycles 4 and 5. Cycle 1: Non treatment for everyone **Groups:** **G1:** Mefenamic acid **G2:** Placebo **Followup:** 5 months	**Inclusion criteria:** • Menorrhagia (mean MBL of 80 ml or more per cycle or history of prolonged or profuse menses that warranted medical and/or surgical intervention) • Regular menstrual cycles **Exclusion criteria:** See inclusion criteria **N at enrollment:** **G1+G2:** 14 **N at followup:** **G1+G2:** 10 **Age:** NR **BMI**: NR **Race/ethnicity**: NR **Parity:** NR	NR[b]	**Bleeding:** MBL measured by the alkaline hematin method reduction during treatment cycle, n: **G1+G2:** 8/10 MBL reduction during treatment cycle vs. non treatment cycle, n: **G1+G2:** p<0.05 Endometrial prostaglandin levels lower during treatment cycle, n: **G1+G2:** 9/10 **Quality of life:** NR **Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions, n:** Hysterectomy: **G1+G2:** 1/14 Combined oral contraceptive: **G1+G2:** 1/14	**Overall quality:** Poor **Risk of bias:** Randomization: Unclear Allocation concealment: Unclear Selective reporting: Low Blinding patients/personnel: Low Blinding outcome assessment: Low Incomplete outcome reporting: High Other: Low

Table Notes: [a] Mefenamic acid was a gift of Parke-Davis; [b] Results only displayed graphically.

AUB KQ1 Evidence Table (Reference ID #1059)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Van Eijkeren et al., 1992 **Country:** Netherlands **Enrollment period:** NR **Intervention setting:** Hospital **Funding:** NR **Author industry relationship disclosures:** NR **Study Design:** RCT **Blinding:** Patients, clinicians	**Intervention:** Mefenamic acid (Ponstan) 500 mg, 3 times per day starting 5 days before expected menstrual cycle date until menstrual bleeding arrested. **Comparator:** Placebo, 3 times per day **Groups:** **G1:** Mefenamic acid **G2:** Placebo **Followup:** One control cycle, one medicated cycle, hysterectomy at following cycle	**Inclusion criteria:** Aged <45 years • Scheduled hysterectomy Measured menstrual blood loss >80ml Regular menstrual cycle **Exclusion criteria:** Use of intrauterine device Use of NSAIDs or medications interfering with homeostasis Contraindications against use of NSAIDS, such as liver or kidney function impairments, stomach ulcers, or asthmatic bronchitis Use of hormonal medications **N at enrollment:** **G1+G2:** 19 **N at followup:** **G1:** 6 **G2:** 5 **Age, mean years ± SD:** **G1:** 39.8 ± 3.6 **G2:** 39.4 ± 3.0 **BMI:** NR **Parity:** NR **Race/ethnicity:**	**Bleeding:** MBL, mean ml ± SD: **G1:** 108 ± 27 **G2:** 151 ± 46 **G1 vs. G2:** p=0.09	**Bleeding:** MBL, mean ml ± SD: **G1:** 65 ± 19 **G2:** 189 ± 69 **G1 vs. BL:** p=0.01 **G2 vs. BL:** p=0.46 **Other:** Midluteal progesterone level, mean nmol/l ± SD: **G1:** 27.3 ± 14.9 **G2:** 40.6 ± 19.8 Progesterone level at operation, mean nmol/l ± SD: **G1:** 4.7 ± 3 **G2:** 3.8 ± 3.5 Plasma levels of mefenamic acid at medicated cycle, mean mcg/ml ± SD: **G1:** 4.39 ± 3.09 **G2:** NA Plasma levels of mefenamic acid at operation, mean mcg/ml ± SD: **G1:** 2.69 ± 4.44 **G2:** NA Interval between onset of menstruation and operation, mean ± SD: **G1:** 10.5 ± 5.2 **G2:** 13.4 ± 5.8 **G1 vs. G2:** p=NS **Quality of life:** NR	**Overall quality:** Fair **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Low Blinding patients/personnel: Low Blinding outcome assessment: Low Incomplete outcome reporting: High Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		NR		**Pain:** NR **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR **Time to conception:** NR **Additional interventions:** NR **Adverse events:** Discontinued medication because of severe skin rash and itching, n: **G1:** 1 **G2:** 0	

AUB KQ1 Evidence Table (Reference ID #1179)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Vargyas et al., 1987 **Country:** United States **Enrollment period:** NR **Intervention setting:** Academic medical center **Funding:** NR **Author industry relationship disclosures:** NR **Study Design:** RCT (crossover) **Blinding:** Patients, clinicians	**Intervention:** Meclofenamate sodium (meclomen), 100 mg three times per day for two cycles followed by placebo for two cycles **Comparator:** Placebo, three times per day for two cycles, followed by meclomen for two cycles Medication initiated after onset of menses and continued for 6 days or until end of menses whichever came first **Groups:** **G1:** Meclomen first then placebo **G2:** Placebo first thenmeclomen **Ga:** Meclomen **Gb:** Placebo **Followup:** Observation phase: 2 months Treatment phase: 2 months	**Inclusion criteria:** • Aged 16 to 42 years History of menorrhagia >60 ml in one observation cycle Negative pregnancy test **Exclusion criteria:** Anovulatory cycles (proliferative endometrium) Histological evidence of pathological changes in the endometrium (hyperplasia or atypia) Extrauterine disease Palpable leiomyoma Known sensitivity to fenamates Anticoagulant therapy Thyroid dysfunction Hepatic disease Renal disease Abnormal cervical cytological findings **N at enrollment:** **G1:** 15 **G2:** 17 **N at follow-up:** **G1:** 13 **G2:** 16 **Age, mean years (range):** **G1:** 36.4 (19, 45) **G2:** 35.3 (29, 43) **Race/ethnicity, n:** White:	**Bleeding:** MBL measured by alkaline hematin method, mean ml (SE): **G1:** 141 (17.5) **G2:** 141.8 (26.5) **G1+G2**: 141.6 (15.9) Number of bleeding days per cycle, mean (SE): **G1+G2:** 6.3 (0.41) Hemoglobin, median gm/dl: **G1+G2:** 13.2 Hematocrit, median %: **G1+G2:** 39.4 Ferritin, median ng/ml: **G1+G2:** 16.0	**Bleeding:** MBL measured by alkaline hematin method, during treatment and placebo cycles, mean ml (SE): **Ga:** 69.0 (6.34) **Gb:** 135.6 (11.3) MBL % change during treatment and placebo cycles from baseline, mean (SE): **Ga:** -48.9 (3.7) **Gb:** -9.2 (5.3) **Ga vs. Gb:** p<0.0001 Number of bleeding days per cycle, mean (SE): **Ga:** 4.8 (0.20) **Gb:** 5.4 (0.18) **Ga vs. BL:** p<0.0003 **Gb vs. BL:** p=NS **Ga vs. Gb:** p<0.0003 Number of pads/tampons used, mean (SE): **Ga:** 15.5 (0.9) **Gb:** 27.6 (2.1) **Ga vs. BL:** p<0.0001 **Gb vs. BL:** p=NS **Ga vs. Gb:** p<0.0001 Hemoglobin, gm/dl, median: **G1+G2:** 12.8 **G1+G2 vs. BL:** p=NS Hematocrit, %, median: **G1+G2:** 38.9 **G1+G2 vs. BL:** p=NS	**Overall Quality:** Good **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Low Blinding patients/personnel: Low Blinding outcome assessment: Low Incomplete outcome reporting: Low Other: Low

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
		G1: 12 **G2:** 13 Black: **G1:** 3 **G2:** 3 **BMI:** NR **Weight, mean pounds (range):** **G1:**149.3 (108, 213) **G2:** 164.7 (120, 130) **Parity:** **G1+G2:** All but 4 patients had one or more living children **Contraception, n (%):** Intrauterine device: **G1+G2:** 7 (21) Previous sterilization: **G1+G2:** 6 (18) Barrier methods: **G1+G2:** 2 (15) Partners with vasectomies or not sexually active: **G1+G2:** 11 **Dysmenorrhea, n (%):** Severe: **G1+G2:** 10 (31) Moderate: **G1+G2:** 16 (50) Dysmenorrheic: **G1+G2:** 6 (18)		Ferritin, ng/ml, median: **G1+G2:** 14.8 **G1+G2 vs. BL:** p=NS **Quality of life:** NR **Pain:** Menstrual symptom severity assessed by patient rating,[a] mean score per cycle: Dysmenorrhea: **Ga:** 0.89 **Gb:** 1.38 **Ga vs. Gb:** p<0.006 Backache: **Ga:** 0.20 **Gb:** 0.50 **Ga vs. Gb:** p<0.02 Headache: **Ga:** 0.25 **Gb:** 0.63 **Ga vs. Gb:** p<0.002 Nausea: **Ga:** 0.13 **Gb:** 0.17 **Ga vs. Gb:** p=NS Vomiting: **Ga:** 0.0 **Gb:** 0.05 **Ga vs. Gb:** p=NS **Sexual function:** NR **Patient satisfaction:** NR **Fertility:** NR	

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
				Time to conception: NR **Additional interventions:** NR **Adverse events[b]:** Nausea/vomiting, n: **Ga:** 4 **Gb:** NR Epigastric distress, n: **Ga:** 1 **Gb:** NR	

Table Notes: [a] Patient rated on a daily basis from none=0 to severe=3; [b] One patient discontinued the study because of gastric distress after one cycle of Meclomen. Two patients discontinued after screening phase for personal reasons.

AUB KQ1 Evidence Table (Reference ID #415, #379)

Study Description	Intervention(s)/ Comparator(s)	Patient Population	Baseline Measure(s)	Outcome Measure(s)	Overall Quality Risk of Bias
Author: Vuorma et al., 2004 Vuorma et al., 2003 **Country:** Finland **Enrollment period:** January 1997 to September 1999 **Intervention setting:** Gynecology outpatient clinics at 14 hospitals **Funding:** STAKES, National Research and Development Centre for Welfare and Health, and Public Health Doctoral Programmes of Helsinki and Tempere universities **Author industry relationship disclosures:** None **Study Design:** RCT **Blinding:** None	**Intervention:** Information group-mailed a decision-aid booklet explaining menorrhagia and risks and benefits of treatment options. **Comparator:** Usual care **Groups:** **G1:** Information **G2:** Control **Followup:** 12 months	**Inclusion criteria:** • Aged 35 to 54 years • Referral for menorrhagia or fibroids • Heavy menstruation as main gynecological complaint **Exclusion criteria:** Symptoms other than heavy menstrual bleeding main cause for medical care **N at enrollment:** **G1:** 184 **G2:** 179 **N at followup:** **G1:** 156 **G2:** 159 **Age, mean years (SE):** **G1:** 44.5 (0.31) **G2:** 44.3 (0.31) **BMI:** NR **Parity:** NR **Race/ethnicity:** NR **Education <12 years, n (%):** **G1:** 104 (57) **G2:** 94 (53)	Inconvenience due to heavy bleeding,[a] mean (SE): **G1:** 19.2 (0.34) **G2:** 19.5 (0.35) Menstrual pain,[b] mean (SE): **G1:** 4.9 (0.27) **G2:** 4.7 (0.27) Periods perceived as very heavy, n (%): **G1:** 112 (61) **G2:** 115 (64) Irregular periods, n (%): **G1:** 42 (23) **G2:** 46 (26) Pelvic pain or pressure, n (%): **G1:** 86 (47) **G2:** 80 (45) Anxiety,[c] mean (SE): **G1:** 36.1 (0.80) **G2:** 35.9 (0.81) Inconvenience due to heavy bleeding,[ad] mean (SE): **G1:** 19.1 (0.38) **G2:** 19.5 (0.37) Menstrual pain,[bd] mean (SE): **G1:** 4.8 (0.29) **G2:** 4.7 (0.29) Anxiety,[cd] mean (SE): **G1:** 36.0 (0.85) **G2:** 35.8 (0.85)	Satisfaction with communication with personnel in gynecology outpatient clinics,[i] median (IQR): **G1:** 36 (30, 39) **G2:** 36.5 (31, 40) **G1 vs. G2:** p=0.6 Change in anxiety level at 3 months, median (IQR): **G1:** 1 (-5, 5) **G2:** -1 (-4, 4) **G1 vs. G2:** p=0.3 Increase in treatment methods mentioned (max 6) between follow-up and baseline, mean (SE): **G1:** 0.48 (0.102) **G2:** 0.45 (0.102) **G1 vs. G2:** p=0.8 Treatment planned after 3 months, n (%): Hysterectomy: **G1:** 99 (54) **G2:** 85 (49) **G1 vs. G2:** p=0.2 Minor surgery or LNG-IUS: **G1:** 38 (21) **G2:** 52 (29) **G1 vs. G2:** p=0.06 Change in birth control method: **G1:** 4 (2) **G2:** 3 (2) **G1 vs. G2:** p=1.0 Oral medication: **G1:** 33 (18)	**Overall quality:** Poor **Risk of bias:** Randomization: Low Allocation concealment: Low Selective reporting: Low Blinding patients/personnel: High Blinding outcome assessment: High Incomplete outcome reporting: Low Other: Low

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				G2: 15 (8) **G1 vs. G2:** p=0.007 No treatment decision: **G1:** 8 (4) **G2:** 20 (11) **G1 vs. G2:** p=0.02 No visit to outpatient clinic: **G1:** 2 (1) **G2:** 4 (2) **G1 vs. G2:** p=0.4	
			Rand-36 scores,[d] mean (SE): General health: **G1:** 66 (1.5) **G2:** 67 (1.5) Physical functioning: **G1:** 86 (1.3) **G2:** 85 (1.3) Emotional well-being: **G1:** 69 (1.6) **G2:** 69 (1.5) Social functioning: **G1:** 75 (1.9) **G2:** 74 (1.8) Energy: **G1:** 55 (1.8) **G2:** 55 (1.8) Pain: **G1:** 68 (1.8) **G2:** 69 (1.8) Role functioning/physical: **G1:** 65 (3.0) **G2:** 67 (3.0) Role functioning/emotional: **G1:** 64 (3.1) **G2:** 72 (3.1)	Actual treatment received up to 12 months after first visit, n (%): Hysterectomy: **G1:** 98 (53) **G2:** 88 (49) **G1 vs. G2:** p=0.4 Minor surgery or LNG-IUS: **G1:** 30 (16) **G2:** 46 (26) **G1 vs. G2:** p=0.03 Other: **G1:** 54 (29) **G2:** 44 (25) **G1 vs. G2:** p=0.3 No treatment and no visit to outpatient clinic: **G1:** 2 (1) **G2:** 1 (1) **G1 vs. G2:** p=0.4	
			Perceived health VAS, mean (SE): **G1:** 73 (1.4) **G2:** 73 (1.4)	Number of surgical procedures used within 1 year, mean (SE): **G1:** 0.70 (0.04) **G2:** 0.73 (0.04) **G1 vs. G2:** p=0.6	
			Psychosomatic symptoms,[de] mean (SE): **G1:** 31.8 (0.59) **G2:** 32.1 (0.58)	Rand-36 scores, mean change (SE):	
			Sexual satisfaction,[df] women with partners, mean (SE): **G1:** 23.7 (0.42)		

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			G2: 24.2 (0.42) Sexual problems,[dg] women with partners, mean (SE): **G1:** 4.70 (0.20) **G2:** 4.33 (0.20) Partner satisfaction,[dh] women with partners, mean (SE): **G1:** 17.1 (0.27) **G2:** 17.1 (0.27)	General health: **G1:** 2.2 (1.23) **G2:** 2.8 (1.22) **G1 vs. BL:** p=0.07 **G2 vs. BL:** p=0.03 **G1 vs. G2:** p=0.7 Physical functioning **G1:** 2.4 (1.33) **G2:** 2.2 (1.32) **G1 vs. BL:** p=0.04 **G2 vs. BL:** p=0.1 **G1 vs. G2:** p=0.9 Emotional well-being: **G1:** 4.7 (1.40) **G2:** 5.3 (1.39) **G1 vs. BL:** p=0.001 **G2 vs. BL:** p<0.001 **G1 vs. G2:** p=0.7 Social functioning: **G1:** 5.2 (1.98) **G2:** 7.1 (1.96) **G1 vs. BL:** p=0.01 **G2 vs. BL:** p<0.001 **G1 vs. G2:** p=0.5 Energy: **G1:** 8.9 (1.72) **G2:** 8.8 (1.71) **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.001 **G1 vs. G2:** p=0.9 Pain: **G1:** 6.5 (1.96) **G2:** 6.2 (1.95) **G1 vs. BL:** p=0.002 **G2 vs. BL:** p=0.001 **G1 vs. G2:** p=0.9 Role functioning/physical: **G1:** 9.2 (3.41) **G2:** 6.3 (3.38) **G1 vs. BL:** p=0.007 **G2 vs. BL:** p=0.07	

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				G1 vs. G2: p=0.5 Role functioning/emotional: **G1:** 12.6 (3.13) **G2:** 1.9 (3.09) **G1 vs. BL:** p<0.001 **G2 vs. BL:** p=0.5 **G1 vs. G2:** p=0.01 Perceived health VAS, mean change (SE): **G1:** 2.6 (1.38) **G2:** 3.6 (1.36) **G1 vs. BL:** p=0.09 **G2 vs. BL:** p=0.003 **G1 vs. G2:** p=0.6 Psychosomatic symptoms,[e] mean change (SE): **G1:** 3.4 (53) **G2:** 3.8 (0.53) **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.001 **G1 vs. G2:** p=0.5 Inconvenience due to heavy bleeding,[a] mean change (SE): **G1:** 10.4 (0.58) **G2:** 10.5 (0.57) **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.001 **G1 vs. G2:** p=0.9 Menstrual pain,[b] mean change (SE): **G1:** 4.7 (0.29) **G2:** 4.6 (0.29) **G1 vs. BL:** p<0.001 **G2 vs. BL:** p<0.001 **G1 vs. G2:** p=0.8	

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				Anxiety,[c] mean change (SE): **G1:** 2.0 (0.78) **G2:** 1.0 (0.78) **G1 vs. BL:** p=0.012 **G2 vs. BL:** p=0.199 **G1 vs. G2:** p=0.4 Sexual satisfaction,[f] women with partners, mean change (SE): **G1:** 0.29 (0.37) **G2:** -0.14 (0.36) **G1 vs. BL:** p=0.487 **G2 vs. BL:** p=0.688 **G1 vs. G2:** p=0.4 Sexual problems,[g] women with partners, mean change (SE): **G1:** -0.23 (0.18) **G2:** -0.15 (0.18) **G1 vs. BL:** p=0.224 **G2 vs. BL:** p=0.444 **G1 vs. G2:** p=0.8 Partner satisfaction,[h] women with partners, mean change (SE): **G1:** -0.08 (0.18) **G2:** -0.13 (0.18) **G1 vs. BL:** p=0.659 **G2 vs. BL:** p=0.436 **G1 vs. G2:** p=0.9 Satisfaction with outcome of treatment VAS, median (IQR): **G1:** 94 (75, 100) **G2:** 95 (75, 100) **G1 vs. G2:** p=0.9	

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Table Notes and Comments: [a] Scale 5-25; [b] Scale for menstrual pain was calculated by multiplying the intensity of pain (0 for no pain to 6 for heaviest possible pain) by the frequency of pain (0 for never to 2 for every period); [c] Scale 20-80, higher score indicates higher level of anxiety; [d] Data from subset of women who gave 12-month follow-up information G1 (n=156) and G2 (n=159); [e] Scale 18-72; [f] Scale 5-35; [g] Scale 2-14; [h] Scale 3-21; [i] Scale 8-40.

Appendix K. Reasons for Exclusion (KQ1)

Exclusion Code	Exclusion Reason	Count
X-1	Not original research (e.g. review articles, systematic reviews, editorials, commentaries, letters to editor, etc.).	74
X-2	Not published in English language.	0
X-3	Not eligible study design (i.e., not a randomized controlled trial).	430
X-4	Study is basic science, anatomy, imaging, prevalence, physiology, diagnostic, biomarker, or biological mechanism study only.	700
X-5	Does not address key question/other (e.g., intervention unlikely to be used in the primary care setting; intervention not approved for use in the U.S.; bleeding related to pregnancy; acute/emergent bleeding, etc.).	1273
X-6	Study population consists of 20 percent or more women whose bleeding is caused by: structural abnormality (e.g., fibroids, polyps, adenomyosis); cancer; medication side effect; endometrial hyperplasia; or systemic disease (e.g., thyroid disease, coagulopathy).	300
X-7	Study population consists of post-menopausal women.	249
X-8	Study evaluates surgical or invasive intervention(s) only or surgical or invasive intervention is the only comparator**.**	220
X-9	Study evaluates contraceptive efficacy or effectiveness only.	621
X-10	Study does not report baseline and outcome data for a study population with ≥80 percent women in the target population or a subset of women in the target population.	87
X-11	Unable to obtain	4
X-12	Duplicate	1

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Appendix L. Reasons for Exclusion (KQ2)

Exclusion code	Exclusion reason	Count
X-1	Not original research (e.g. review articles, systematic reviews, editorials, commentaries, letters to editor, etc.).	104
X-2	Does not include data from a population of 1600 or more.	1916
X-3	Reporting of harms is from a general population or reporting of harms is not an objective of the paper/study.	913
X-4	Does not report harms data for a selected intervention included in KQ1 (i.e., LNG-IUS; progestogen; tranexamic acid; cabergoline; ethamsylate; exenatide; metformin).	2044
X-5	Study is basic science, anatomy, imaging, prevalence, physiology, diagnostic, biomarker, or biological mechanism study only.	4
X-6	Study of men only.	17
X-7	Study population consists of post-menopausal women or a population aged over 65 years.	101
X-8	Other	26
X-11	Unable to obtain	4
X-12	Duplicate	0

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2705. Zziwambazza W, Merkle CJ, Moore IM, et al.; The effects of norepinephrine infusion on the circulating lymphocyte counts of post-open heart surgery patients. Biol Res Nurs. 2000 Jan;1(3):199-209. PMID: 11232215. ***X-2, X-4***

Appendix M. Labeled Indications for Drugs Included in Review

Generic Name, Route of Administration	Brand Name(s) (approval date)[1]	Labeled Indications[1]
Intrauterine Device		
Levonorgestrel-releasing intrauterine system (52 mg, releasing ~0.02 mg/day) (LNG-IUS; intrauterine device)	Mirena®[2] (December 6, 2000)	• Intrauterine contraception for up to 5 years. • Treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception. Mirena [package insert]. Wayne, NJ: Bayer HealthCare Pharmaceuticals; 2009. Daily Med (Mirena) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=92231d6f-f4d8-43b0-aa95-f7cec1cc18c5
Contraceptive vaginal ring (etonogestrel/ethinyl estradiol vaginal ring, delivers 0.120 mg/0.015 mg per day)	NuvaRing®[2] (October 3, 2001)	• Prevention of pregnancy. NuvaRing [package insert]. Whitehouse Station, NJ: Merck & Co; 2012. DailyMed (NuvaRing) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=017343fb-86c4-45ab-9c47-52cc5b9f3a02
Antifibrinolytic Agents		
Tranexamic acid (650 mg) (oral)	Lysteda®[2] (November 13, 2009)	• Treatment of cyclic heavy menstrual bleeding. Lysteda [package insert]. Parsippany, NJ: Ferring Pharmaceutical; 2011. DailyMed (Lysteda) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=84a65305-65d7-e7fd-66f3-dda8d8f920b1
Combined Oral Contraceptive Agents (COCs)		
Estradiol valerate and dienogest (oral) 28 tablets in the following order: 2 tablets of 3 mg EV; 5 tablets of 2 mg EV and 2 mg D; 17 tablets of 2 mg EV and 3 mg D; 2 tablets of 1 mg EV; and 2 inert tablets.	Natazia®[2] (May 6, 2010)	• Prevent pregnancy. • Treatment of heavy menstrual bleeding in women without organic pathology who choose to use an oral contraceptive as their method of contraception. Natazia [package insert]. Wayne, NJ: Bayer HealthCare Pharmaceuticals; 2012. DailyMed (Natazia) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=02c91fba-9c47-43ef-ac78-e82369798834

Generic Name, Route of Administration	Brand Name(s) (approval date)[1]	Labeled Indications[1]
Ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg) (oral) 28 tablets: 21 tablets of 0.030 mg EE and 0.15 mg L; and 7 inert tablets.	Nordette-28®[2] (July 21, 1982) Levora®[3] (December 13, 1993) Portia-28®[3] (May 23, 2002) Altavera®[3] (August 2, 2010) Marlissa®[3] (February 29, 2012)	• Prevention of pregnancy. Nordette [package insert]. Sellersville, PA: Teva Pharmaceuticals; 2010. DailyMed (Nordette) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=ef68258d-9d09-43c9-af87-bfa4b3b0ee01
Ethinyl estradiol (0.020 mg) and norethindrone acetate (1 mg) (oral) 21 tablets of 0.020 mg EE and 1 mg N. Also available as 28-day regimen with additional 7 tablets containing 75 mg ferrous fumarate (Loestrin Fe 1/20).	Loestrin 21 1/20®[3] (October 1, 1976) Microgestin 1/20®[3] (February 5, 2001) Junel 1/20®[3] (May 30, 2003) Minestrin 1/20®[4]	Loestrin: • For the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception. Minestrin: • For the control of contraception. Loestrin [package insert]. Pomona, NY: Barr harmaceuticals; 2009. DailyMed (Loestrin) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=f40605cf-9933-40d9-915a-ea6dbc0f169f Minestrin 1/20 [package insert]. Fajardo, Puerto Rico: Warner Chilcott; 2006.

Generic Name, Route of Administration	Brand Name(s) (approval date)[1]	Labeled Indications[1]
Norgestimate ethinyl estradiol, triphasic (oral) 28 tablets: 7 tablets of 0.180 mg N and 0.035 mg EE; 7 tablets of 0.215 mg N and 0.035 mg EE; 7 tablets of 0.250 mg N and 0.035 mg EE; and 7 inert tablets.	Ortho Tri-Cyclen®[2] (July 3, 1992) Tri-Sprintec®[3] (December 29, 2003) Tri-Previfem®[3] (March 26, 2004) *LexiComp[5] lists additional brand names. Only those detailed here are listed by the FDA as therapeutic equivalents.* TriNessa *is not listed in Drugs@FDA, but it does appear to be available in the US (drugstore.com).*	Ortho Tri-Cyclen[2] and Tri-Previfem[3]: • Prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception. • Treatment of moderate acne vulgaris in females at least 15 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche. [The drug] should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control. Tri-Sprintec[3] labeling differs slightly on second indication: • Treatment of moderate acne vulgaris in females, ≥15 years of age, who have no known contraindications to oral contraceptive therapy, desire contraception, have achieved menarche and are unresponsive to topical anti-acne medications. Ortho Tri-Cyclen [package insert]. Raritan, NJ: Ortho-McNeil-Janssen Pharmaceuticals; 2010. DailyMed (Ortho Tri-Cyclen) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=384e7a40-dcbd-4908-bf5e-65abc9932973 Tri-Sprintec [package insert]. Pomona, NY: Barr Laboratories; 2009. DailyMed (Tri-Sprintec) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=843cbef6-cbfb-4a44-bb80-22930753e4c0 Tri-Previfem [package insert]. Huntsville, AL: Qualitest Pharmaceuticals; 2011. DailyMed (Tri-Previfem) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=dd15dbd7-75b7-416e-af55-1e90c2bab051
Progestogens		
Dydrogesterone (10 mg) (oral)	Gynorest International brand names[5]: Dabroston; Dufaston; Duphaston; Terolut *NOTE: Dydrogesterone is not currently available in the United States; the FDA lists the marketing status of dydrogesterone (Gynorest) as discontinued. The drug is available in other countries.*	Reported use[5]: Treatment of progesterone deficiencies; counteract unopposed estrogen in hormone replacement therapy.

Generic Name, Route of Administration	Brand Name(s) (approval date)[1]	Labeled Indications[1]
Medroxyprogesterone acetate (400 mg/mL) (injectable suspension)	Depo-Provera CI®[2] (October 29, 1992) Depo-subQ Provera 104®[2] (December 17, 2004)	Depo-Provera CI: • Prevention of pregnancy. Depo-subQ Provera 104: • Prevention of pregnancy in women of child bearing potential. • Management of endometriosis-associated pain. Depo-Provera CI [package insert]. New York City, NY: Parmacia and Upjohn; 2011. DailyMed (Depo-Provera) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=199cf13e-0859-4a73-9b45-e700d0cd1049 Depo-subQ Provera 104 [package insert]. New York City, NY: Pharmacia and Upjohn; 2011. DailyMed (Depo-subQ Provera) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=390087a6-f3c3-4f0b-a930-79acf412f153
Medroxyprogesterone acetate (2.5 mg, 5 mg, or 10 mg) (oral)	Provera®[2] (June 18, 1959)	• Treatment of secondary amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer. • Reduce the incidence of endometrial hyperplasia in nonhysterectomized postmenopausal women receiving daily oral conjugated estrogens 0.625 mg tablets. Provera [package insert]. New York City, NY: Pharmacia and Upjohn; 2009. DailyMed (Provera) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a586be28-96af-4fed-a13f-9b94fd4c7405
Norethisterone [norethindrone] (5 mg) (oral)	Aygestin®[2] (April 21, 1982)	• Treatment of secondary amenorrhea, endometriosis, and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer. Aygestin [package insert]. Pomona, NY: Duramed Pharmaceuticals; 2010. DailyMed (Aygestin) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=69f5bc4b-758d-471b-ad8d-17c94f8e0963
Progesterone (4% [45 mg] or 8% [90 mg]) (vaginal gel)	Crinone®[2] (July 31, 1997)	• Progesterone supplementation or replacement as part of an Assisted Reproductive Technology ("ART") treatment for infertile women with progesterone deficiency. • Secondary amenorrhea. Crinone [package insert]. Morristown, NJ: Watson Pharma; 2011. DailyMed (Crinone) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=2c8ffbd2-6b7a-42c7-b29e-e4de69dad9e6

Generic Name, Route of Administration	Brand Name(s) (approval date)[1]	Labeled Indications[1]
Progesterone (0.065 mg/day, according to multiple sources) (coil/intrauterine insert)	Progestasert (February 4, 1976) *NOTE: The FDA lists the marketing status of Progestasert as discontinued as of June 1, 2001.*	• Prevention of pregnancy.
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)		
Flurbiprofen (50 mg or 100 mg) (oral)	Ansaid®[2] (October 31, 1988)	• For relief of the signs and symptoms of rheumatoid arthritis. • For relief of the signs and symptoms of osteoarthritis. Ansaid [package insert]. New York City, NY: Pfizer / Pharmacia & Upjohn Co.; 2010. DailyMed (flurbiprofen) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=f56be63c-88e4-4b78-b12d-d80e3e8b3893
Meclofenamate sodium (50 mg or 100 mg) (oral)	Meclomen (June 25, 1980) *NOTE: The FDA lists the marketing status of Meclomen as discontinued. The drug is available in the US as generic.*	• For the relief of mild to moderate pain. • For the treatment of primary dysmenorrhea and for the treatment of idiopathic heavy menstrual blood loss. • For relief of the signs and symptoms of acute and chronic rheumatoid arthritis and osteoarthritis. Meclofenamate sodium [package insert]. Morgantown, WV: Mylan Pharmaceuticals; 2006. DailyMed (meclofenamate sodium) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=96f19af4-de8f-4fd7-90d8-55fe6ebdd81d
Mefenamic acid (250 mg) (oral)	Ponstel®[2] (March 28, 1967)	• For relief of mild to moderate pain in patients ≥14 years of age, when therapy will not exceed one week (7 days). • For treatment of primary dysmenorrhea. Ponstel [package insert]. Atlanta, GA: Sciele Pharma; 2008. DailyMed (Ponstel) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=d77e13db-d1b1-4dbf-9de8-80827018cf43

Generic Name, Route of Administration	Brand Name(s) (approval date)[1]	Labeled Indications[1]
Naproxen sodium (oral) Naprosyn as 250 mg, 375 mg, or 500 mg tablets; Anaprox as 275 mg tablets; Anaprox DS as 550 mg tablets; others available.	Naprosyn®[2] (March 11, 1976) Anaprox DS®[2] (September 4, 1980) Anaprox®[3] (September 4, 1980) Naprosyn Suspension®[2] (March 23, 1987) EC-Naprosyn®[2] (October 14, 1994) *Also various OTC brands*	Naprosyn, EC-Naprosyn, Anaprox, Anaprox DS, and Naprosyn Suspension is indicated: • For the relief of the signs and symptoms of rheumatoid arthritis. • For the relief of the signs and symptoms of osteoarthritis. • For the relief of the signs and symptoms of ankylosing spondylitis. • For the relief of the signs and symptoms of juvenile arthritis. Naprosyn, Anaprox, Anaprox DS, and Naprosyn Suspension is also indicated: • For relief of the signs and symptoms of tendonitis. • For relief of the signs and symptoms of bursitis. • For relief of the signs and symptoms of acute gout. • For the management of pain. • For the management of primary dysmenorrheal. EC-Naprosyn / Naprosyn / Anaprox / Anaprox DS / Naprosyn [package insert]. Nutley, NJ: Roche Pharmaceuticals; 1999-200X. DailyMed (Naprosyn) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=68848217-03c9-4377-9be6-6f567e629129
Other Drugs		
Cabergoline (0.5 mg) (oral)	Dostinex (December 23, 1996) *NOTE: The FDA lists the marketing status of Dostinex as discontinued. The drug is available in the US as generic.*	• Treatment of hyperprolactinemic disorders, either idiopathic or due to pituitary adenomas. Cabergoline [package insert]. Sellersville, PA: Teva Pharmaceuticals; 2011. DailyMed (cabergoline) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=e497366b-a124-4d7f-bd45-a883c392d4bb
Etamsylate [ethamsylate] (250 mg or 500 mg) (oral)	International brand names[5]: Altodor; Dicinone; Dicynene; Dicynone; Eselin; Ethamsyl; Hemo 141; Hemoced; Impedil *NOTE: Etamsylate is not currently available in the United States. The drug is available in other countries.*	Reported use[5]: Prevention and treatment of capillary hemorrhages; treatment of menorrhagia or metrorrhagia.
Exenatide (0.25 mg/mL as either 0.005 mg or 0.01 mg per dose) (injection)	Byetta®[2] (April 28, 2005)	• As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Byetta [package insert]. San Diego, CA: Amylin Pharmaceuticals; 2011. DailyMed (Byetta) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=751747da-7c1f-41ad-b1a6-a6d920f70599

Generic Name, Route of Administration	Brand Name(s) (approval date)[1]	Labeled Indications[1]
Metformin hydrochloride (oral) Glucophage as 500 mg, 850 mg, or 1000 mg tablets; Glucophage XR as 500 mg or 750 mg tablets; Fortamet and Glumetza as 500 mg or 1000 mg tablets.	Glucophage®[2] (March 3, 1995) Glucophage XR®[2] (October 13, 2000) Fortamet®[2] (April 28, 2004) Glumetza®[2] (June 3, 2005)	• As an adjunct to diet and exercise to improve glycemic control in adults and children with type 2 diabetes mellitus. Glucophage [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2009. DailyMed (Glucophage) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=4a0166c7-7097-4e4a-9036-6c9a60d08fc6
N-acetyl-cysteine (oral; also available as solution for inhalation, IV injection, or ocular solution)	Mucomyst (September 14, 1963; marketing discontinued) Acetadote®[2] (injectable, IV) (January 23, 2004) Acetylcysteine is also available in tablet form as a dietary supplement under various brand names.	• Prevent or lessen hepatic injury after ingestion of acetaminophen (acute poisoning or repeated supratherapeutic ingestion). • Adjuvant therapy for patients with abnormal, viscid, or inspissated mucous secretions in conditions such as: chronic broncopulmonary disease; acute bronchopulmonary disease; pulmonary complications of cystic fibrosis; tracheostomy care; pulmonary complications associated with surgery; during anesthesia, post-traumatic chest conditions; atelectasis due to mucous obstruction; and diagnostic bronchial studies. Acetadote [package insert]. Nashville, TN: Cumberland Pharmaceuticals; 2011. Acetylcysteine solution [package insert]. Lake Forest, IL: Hospira, Inc.; 2004. DailyMed (Acetadote) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=472f158a-5ab9-4308-8e49-1116e6ea3d39 DailyMed (acetylcysteine solution) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=5558a5f5-e821-473b-7d8a-5d33d09f0586

Notes:

[1] US-based information; brand names, therapeutic equivalency, dates of approval, and indications per FDA website (Drugs@FDA) and individual package inserts, unless otherwise noted; last accessed September 4, 2012.

[2] Listed by FDA as the Reference Listed Drug (RLD): an approved drug product to which new generic versions are compared to show that they are bioequivalent.

[3] Listed by FDA as therapeutic equivalent to RLD.

[4] Canadian brand name and approval information.

[5] Lexi-Comp OnlineTM, Lexi-Drugs International OnlineTM, Hudson, Ohio: Lexi-Comp, Inc.; September 4, 2012.

Appendix N. Harms from Package Inserts for Drugs Included in Review

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
Levonorgestrel-releasing intrauterine system (LNG-IUS; Mirena®)	*Warnings and Precautions:* • If pregnancy should occur with Mirena in place, remove Mirena. • There is increased risk of ectopic pregnancy including loss of fertility, pregnancy loss, septic abortion (including septicemia, shock and death) and premature labor and delivery. • Group A streptococcal infection has been reported; strict aseptic technique is essential during insertion. • Before using Mirena, consider the risks of pelvic inflammatory disease (PID). • Bleeding patterns become altered, may remain irregular and amenorrhea may ensue. • Perforation may occur during insertion. Risk is increased in women with fixed retroverted uteri, during lactation, and postpartum. • Embedment in the myometrium and partial or complete expulsion may occur. • Persistent enlarged ovarian follicles should be evaluated. *Serious:* • Ectopic pregnancy - Incidence in clinical trials excluding women with risk factors for ectopic was 0.1% per year. • Intrauterine pregnancy - "As of September 2006, 390 live births out of an estimated 9.9 million Mirena users had been reported." • Group A streptococcal sepsis (GAS) – "As of September 2006, 9 cases of Group A streptococcal sepsis (GAS) out of an estimated 9.9 million Mirena users had been reported." • Pelvic Inflammatory Disease • Embedment • Perforation • Breast cancer – "Spontaneous reports of breast cancer have been received during postmarketing experience with Mirena… Two observational studies have not provided evidence of an increased risk of breast cancer during the use of Mirena." *Most common (≥5% users):* • Uterine/vaginal bleeding alterations (51.9%) • Amenorrhea (23.9%) • Intermenstrual bleeding and spotting (23.4%)	"The data provided reflect the experience with the use of Mirena in the adequate and well-controlled studies for contraception (n=2,339) and heavy menstrual bleeding (n=80). For the contraception indication, Mirena was compared to a copper IUD (n=1,855), to another formulation of levonorgestrel intrauterine system (n=390) and to a combined oral contraceptive (n=94) in women 18 to 35 years old. The data cover more than 92,000 woman-months of exposure. For the treatment of heavy menstrual bleeding indication (n=80), the subjects included women aged 26 to 50 with confirmed heavy bleeding and exposed for a median of 183 treatment days of Mirena (range 7 to 295 days). The frequencies of reported adverse drug reactions represent crude incidences. The adverse reactions seen across the 2 indications overlapped, and are reported using the frequencies from the contraception studies." Mirena [package insert]. Wayne, NJ: Bayer HealthCare Pharmaceuticals; 2009.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Abdominal/pelvic pain (12.8%) • Ovarian cysts (12%) • Headache/migraine (7.7%) • Acne (7.2%) • Depressed/altered mood (6.4%) • Menorrhagia (6.3%) • Breast tenderness/pain (4.9%) • Vaginal discharge (4.9%) • IUD expulsion (4.9%) *Other (<5% users):* • Nausea • Nervousness • Vulvovaginitis • Dysmenorrhea • Back pain • Weight increase • Decreased libido • Cervicitis/Papanicolaou smear normal/class II • Hypertension • Dyspareunia • Anemia • Alopecia • Skin disorders including eczema • Pruritus • Rash and urticaria • Abdominal distention • Hirsutism • Edema *Postmarketing reports of:* • Device breakage • Angioedema	
Contraceptive vaginal ring (NuvaRing®)	*Warning:* Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptive use. This risk increases with age, particularly in women over 35 years of age and with the number of cigarettes smoked. For this reason, COCs should not be used by women	NuvaRing [package insert]. Whitehouse Station, NJ: Merck & Co; 2012.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	who are over 35 years of age and smoke. *Most common (reported by 5-14% of women in clinical trials:* • Vaginitis • Headache • Upper respiratory infection • Vaginal secretion • Sinusitis • Weight gain • Nausea *Adverse events leading to discontinuation in 1-2.5% of women using NuvaRing in trials:* • Device-related events (foreign body sensation, coital problems, device explusion) • Vaginal symptoms (discomfort/vaginitis/vaginal secretion) • Headache • Emotional lability • Weight gain Also any adverse reactions that are associated with the use of combination hormonal contraceptives are also likely to apply to combination vaginal hormonal contraceptives, such as NuvaRing.	
Tranexamic acid (oral; Lysteda®)	*Warnings and Precautions:* • The risk of thrombotic and thromboembolic events may increase further when hormonal contraceptives are administered with Lysteda, especially in women who are obese or smoke cigarettes. Women using hormonal contraception should use Lysteda only if there is a strong medical need and the benefit of treatment will outweigh the potential increased risk of a thrombotic event. Do not use Lysteda in women who are taking more than the approved dose of a hormonal contraceptive. • Concomitant use of Lysteda with Factor IX complex concentrates, anti-inhibitor coagulant concentrates, or all-trans retinoic acid (oral tretinoin) may increase the risk of thrombosis. • Visual or ocular adverse effects may occur with Lysteda. Immediately discontinue use if visual or ocular symptoms occur. • Cerebral edema and cerebral infarction may be caused by use of Lysteda in women with subarachnoid hemorrhage. • Ligneous conjunctivitis has been reported in patients taking	"Lysteda safety derived from two randomized, double-blind, placebo-controlled studies on treatment of heavy menstrual bleeding. Long-term safety was studied in two open label studies." "In one study, subjects with physician-diagnosed heavy menstrual bleeding (not using the alkaline hematin methodology) were treated with 3900 mg/day for up to 5 days during each menstrual period for up to 27 menstrual cycles. A total of 781 subjects were enrolled and 239 completed the study through 27 menstrual cycles. A total of 12.4% of the subjects withdrew due to adverse events. Women using hormonal contraception were excluded from the study… A long-term open-label extension study of subjects from the two short-term efficacy studies was also conducted in which subjects were treated with 3900 mg/day for up to 5 days during each menstrual

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	tranexamic acid. *From RCTs for HMB:* G1: lysteda group (N=232) G2: placebo group (N=139) Total number of adverse events G1: 1500 G1: 923 Headache, including tension headache G1: 117 (50.4%) G2: 65 (46.8%) Nasal and sinus symptoms, including nasal, respiratory tract and sinus congestion, sinusitis, acute sinusitis, sinus headache, allergic sinusitis, and sinus pain, and multiple allergies and seasonal allergies G1: 59 (25.4%) G2: 24 (17.3%) Back pain G1: 48 (20.7%) G2: 21 (15.1%) Abdominal pain, including abdominal tenderness and discomfort G1:46 (19.8%) G2: 25 (18.0%) Musculoskeletal pain, including musculoskeletal discomfort and myalgia G1: 26 (11.2%) G2: 4 (2.9%) Arthralgia, including joint stiffness and swelling G1: 16 (6.9%) G2: 7 (5.0%) Muscle cramps and spasms G1: 15 (6.5%) G2: 8 (5.8%) Migraine G1: 14 (6.0%) G2: 8 (5.8%) Anemia G1: 13 (5.6%) G2: 5 (3.6%) Fatigue G1: 12 (5.2%) G2: 6 (4.3%) *Postmarketing reports in patients receiving tranexamic acid for various*	period for up to 9 menstrual cycles. A total of 288 subjects were enrolled and 196 subjects completed the study through 9 menstrual cycles. A total of 2.1% of the subjects withdrew due to adverse events… The types and severity of adverse events in these two long-term open-label trials were similar to those observed in the double-blind, placebo-controlled studies although the percentage of subjects reporting them was greater in the 27-month study, most likely because of the longer study duration." Lysteda [package insert]. Parsippany, NJ: Ferring Pharmaceutical; 2011.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	indications: • Nausea, vomiting, and diarrhea • Allergic skin reactions • Anaphylactic shock and anaphylactoid reactions • Thrombotic events (e.g., deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical necrosis, and central retinal artery and vein obstruction) – including venous and arterial thrombotic events in women who have used Lysteda concomitantly with combined hormonal contraceptives • Impaired color vision and other visual disturbances • Dizziness	
0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel (oral; Nordette-28®, others)	*Warning:* Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke. *Reported in patients taking oral contraceptives and believed to be drug-related:* • Nausea • Vomiting • Gastrointestinal symptoms (such as abdominal pain, cramps and bloating) • Breakthrough bleeding • Spotting • Change in menstrual flow • Amenorrhea • Temporary infertility after discontinuation of treatment • Edema/fluid retention • Melasma/chloasma which may persist • Breast changes: tenderness, pain, enlargement, secretion • Change in weight or appetite (increase or decrease) • Change in cervical erosion and secretion • Diminution in lactation when given immediately postpartum • Cholestatic jaundice • Rash (allergic) • Mood changes, including depression • Vaginitis, including candidiasis • Change in corneal curvature (steepening)	"The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30." "Case control studies have found the relative risk of users compared to non-users to be 3 for the first episode of superficial venous thrombosis, 4 to 11 for deep-vein thrombosis or pulmonary embolism, and 1.5 to 6 for women with predisposing conditions for venous thromboembolic disease. Cohort studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospitalization. The approximate incidence of deep-vein thrombosis and pulmonary embolism in users of low dose (<50µg ethinyl estradiol) combination oral contraceptives is up to 4 per 10,000 woman-years compared to 0.5 to 3 per 10,000 woman-years for non-users. However, the incidence is substantially less than that associated with pregnancy (6 per 10,000 woman-years). The risk of thromboembolic disease due to oral contraceptives is not related to length of use and disappears after pill use is stopped." "In a large study, the relative risk of thrombotic strokes has been shown to range from 3 for normotensive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for nonsmokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Intolerance to contact lenses • Mesenteric thrombosis • Decrease in serum folate levels • Exacerbation of systemic lupus erythematosus • Exacerbation of porphyria • Exacerbation of chorea • Aggravation of varicose veins • Anaphylactic/anaphylactoid reactions, including urticaria, angioedema, and severe reactions with respiratory and circulatory symptoms. *Reported in patients taking oral contraceptives, with association neither confirmed nor refuted:* • Congenital anomalies • Premenstrual syndrome • Cataracts • Optic neuritis, which may lead to partial or complete loss of vision • Cystitis-like syndrome • Nervousness • Dizziness • Hirsutism • Loss of scalp hair • Erythema multiforme • Erythema nodosum • Hemorrhagic eruption • Impaired renal function • Hemolytic uremic syndrome • Budd-Chiari syndrome • Acne • Changes in libido • Colitis • Sickle-cell disease • Cerebral-vascular disease with mitral valve prolapse • Lupus-like syndromes • Pancreatitis • Dysmenorrhea	normotensive users, and 25.7 for users with severe hypertension. The attributable risk is also greater in older women." Nordette [package insert]. Sellersville, PA: Teva Pharmaceuticals; 2010.
estradiol valerate and dienogest (oral; Natazia®)	*Warning:* Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age and with the number of cigarettes smoked. For this reason, COCs should not be used by women	"A total of 2,131 women, 18 to 54 years of age, who took at least one dose of Natazia were enrolled in four clinical phase 3 trials. A total of 1,867 subjects were included in two clinical phase 3 studies with a treatment duration up to 28 cycles with Natazia as an

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	who are over 35 years of age and smoke. *Serious:* • Serious cardiovascular events and stroke • Vascular events • Liver disease *Including reports from clinical trials of:* • Myocardial infarction (2 cases) • Ruptured ovarian cyst (2 cases) • Deep vein thrombosis • Focal nodular hyperplasia of the liver • Uterine leiomyoma • Acute cholecystitis • Chronic acalculous cholecystitis *Commonly reported:* • Irregular uterine bleeding • Nausea • Breast tenderness • Headache *Common (≥2%):* • Headache (including migraines) (12.7%) • Breast pain, discomfort or tenderness (7.0%) • Menstrual disorders (metrorrhagia, menstruation irregular, menorrhagia, vaginal hemorrhage, dysfunctional uterine bleeding, genital hemorrhage, abnormal withdrawal bleeding, uterine hemorrhage) (6.9%) • Nausea or vomiting (6.0%) • Acne (3.9%) • Mood changes (depression, mood swings, depressed mood, mood altered, affect lability, dysthymic disorder, crying) (3.0%) • Increased weight (2.9%) *Led to study discontinuation:* 11.4% of the women discontinued from the clinical trials due to an adverse reaction; the most frequent adverse reactions leading to discontinuation were: • Menstrual disorder (metrorrhagia, menorrhagia, menstruation irregular, genital hemorrhage, vaginal hemorrhage, dysfunctional uterine bleeding) (2.3%)	oral contraceptive and 264 subjects in the two phase 3 clinical trials with a treatment duration of 7 cycles evaluating Natazia in the treatment of heavy, prolonged, and/or frequent menstrual bleeding in women without organic pathology." Natazia [package insert]. Wayne, NJ: Bayer HealthCare Pharmaceuticals; 2012.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Mood changes (depression, mood swings, mood altered, depressed mood, dysthymic disorder, crying) (1.2%) • Acne (1.1%), headache (including migraines) (1.1%) • Weight increased (0.7 %) *Postmarketing experience:* • Vascular disorders: Venous and arterial thromboembolic events (including pulmonary emboli, deep vein thrombosis, cerebral thrombosis, myocardial infarction and stroke), hypertension • Hepatobiliary disorders: Gallbladder disease, hepatitis • Immune system disorders: Hypersensitivity • Metabolism and nutrition disorders: Fluid retention, hypertriglyceridemia • Nervous system disorders: Dizziness • Skin and subcutaneous tissue disorders: Chloasma, angioedema, erythema nodosum, erythema multiforme • Gastrointestinal disorders: Gastrointestinal symptoms (for example, abdominal pain) • Infections and infestations: Vulvovaginal candidiasis	
0.20mg ethinyl estradiol and 1mg norethindrone acetate (oral; Loestrin 21 1/20®, others)	*Warning:* Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke. *Increased risk of serious adverse reactions:* • Thrombophlebitis • Arterial thromboembolism • Pulmonary embolism • Myocardial infarction • Cerebral hemorrhage • Cerebral thrombosis • Hypertension • Gallbladder disease • Hepatic adenomas or benign liver tumors *Evidence of an association between the following conditions and the use of oral contraceptives, although additional confirmatory studies are needed:*	Loestrin [package insert]. Pomona, NY: Barr Pharmaceuticals; 2009. NOTE: package insert includes 89 references, many of which are related to adverse effects.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Mesenteric thrombosis • Retinal thrombosis *Reported in patients receiving oral contraceptives and are believed to be drug-related:* • Nausea • Vomiting • Gastrointestinal symptoms (such as abdominal cramps and bloating) • Breakthrough bleeding • Spotting • Change in menstrual flow • Amenorrhea • Temporary infertility after discontinuation of treatment • Edema • Melasma which may persist • Breast changes: tenderness, enlargement, secretion • Change in weight (increase or decrease) • Change in cervical erosion and secretion • Diminution in lactation when given immediately postpartum • Cholestatic jaundice • Migraine • Rash (allergic) • Mental depression • Reduced tolerance to carbohydrates • Vaginal candidiasis • Change in corneal curvature (steepening) • Intolerance to contact lenses *Reported in users of oral contraceptives and the association has been neither confirmed nor refuted:* • Pre-menstrual syndrome • Cataracts • Changes in appetite • Cystitis-like syndrome • Headache • Nervousness • Dizziness • Hirsutism • Loss of scalp hair • Erythema multiforme	

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Erythema nodosum • Hemorrhagic eruption • Vaginitis • Porphyria • Impaired renal function • Hemolytic uremic syndrome • Budd-Chiari syndrome • Acne • Changes in libido • Colitis	
norgestimate ethinyl estradiol, triphasic (oral; Ortho Tri Cyclen®, others)	*Warning:* Cigarette smoking increases the risk of serious cardiovascular events from combination oral contraceptives (COC) use. This risk increases with age, particularly in women over 35 years of age, and with the number of cigarettes smoked. For this reason, COCs should not be used by women who are over 35 years of age and smoke. *An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives:* • Thrombophlebitis and venous thrombosis with or without embolism • Arterial thromboembolism • Pulmonary embolism • Myocardial infarction • Cerebral hemorrhage • Cerebral thrombosis • Hypertension • Gallbladder disease • Hepatic adenomas or benign liver tumors *There is evidence of an association between the following conditions and the use of oral contraceptives:* • Mesenteric thrombosis • Retinal thrombosis *The following adverse reactions have been reported in patients receiving oral contraceptives and are believed to be drug-related:* • Nausea • Vomiting • Gastrointestinal symptoms (such as abdominal cramps and bloating) • Breakthrough bleeding	Ortho Tri-cyclen [package insert]. Raritan, NJ: Ortho-McNeil-Janssen Pharmaceuticals; 2010. NOTE: package insert includes 101 references, many of which are related to adverse effects.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Spotting • Change in menstrual flow • Amenorrhea • Temporary infertility after discontinuation of treatment • Edema • Melasma which may persist • Breast changes: Tenderness, enlargement, secretion • Change in weight (increase or decrease) • Change in cervical erosion and secretion • Diminution in lactation when given immediately postpartum • Cholestatic jaundice • Migraine • Allergic reaction, including rash, urticaria, angioedema • Mental depression • Reduced tolerance to carbohydrates • Vaginal candidiasis • Change in corneal curvature (steepening) • Intolerance to contact lenses *The following adverse reactions have been reported in users of oral contraceptives and a causal association has been neither confirmed nor refuted:* • Pre-menstrual syndrome • Cataracts • Changes in appetite • Cystitis-like syndrome • Headache • Nervousness • Dizziness • Hirsutism • Loss of scalp hair • Erythema multiforme • Erythema nodosum • Hemorrhagic eruption • Vaginitis • Porphyria • Impaired renal function • Hemolytic uremic syndrome • Acne • Changes in libido	

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Colitis • Budd-Chiari Syndrome	
Dydrogesterone (oral; Gynorest) NOTE: marketing discontinued in US; labels are not available.	As for progestogens in general. Porphyria • The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dydrogesterone as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients. (The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/10/11)) Pregnancy • Anomalies (non-virilising) of the genito-urinary tract were found in a 4-month-old baby whose mother had taken dydrogesterone 20 mg daily from the eighth to twentieth week of pregnancy and 10 mg daily from then until term.1 She had also been given hydroxyprogesterone caproate 250 mg by intramuscular injection weekly from the eighth to the twentieth week. (Roberts IF, West RJ. Teratogenesis and maternal progesterone. Lancet 1977; ii: 982. (PubMed id:72325))	Dydrogesterone. In: Micromedex® Healthcare Series. Thomson Reuters (Healthcare) Inc. http://www.thomsonhc.com (accessed March 31, 2012). Martindale: The Complete Drug Reference. Pharmaceutical Press. Electronic version, Thomson Reuters (Healthcare) Inc. http://www.thomsonhc.com (accessed March 31, 2012).
Medroxyprogesterone acetate (injectable; Depo-Provera CI®, others)	*Warnings:* • Intrauterine exposure: "Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female fetuses. The risk of hypospadias (5 to 8 per 1,000 male births in the general population) may be approximately doubled with exposure to these drugs. There are insufficient data to quantify the risk to exposed female fetuses, but insofar as some of these drugs induce mild virilization of the external genitalia of the female fetus, and because of the increased association of hypospadias in the male fetus, it is prudent to avoid the use of these drugs during the first trimester of pregnancy." • Thromboembolic disorders • Ocular disorders • Lactation *Reported:* • Breakthrough bleeding • Spotting • Change in menstrual flow • Amenorrhea	Depo-Provera CI [package insert]. New York, NY: Pharmacia and Upjohn Company; 2011.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Headache • Nervousness • Dizziness • Edema • Change in weight (increase or decrease) • Changes in cervical erosion and cervical secretions • Cholestatic jaundice, including neonatal jaundice • Breast tenderness and galactorrhea • Skin sensitivity reactions consisting of urticaria, pruritus, edema and generalized rash • Acne, alopecia and hirsutism • Rash (allergic) with and without pruritis • Anaphylactoid reactions and anaphylaxis • Mental depression • Pyrexia • Fatigue • Insomnia • Nausea • Somnolence In a few instances there have been undesirable sequelae at the site of injection, such as residual lump, change in color of skin, or sterile abscess. *The following adverse reactions have been observed in patients receiving estrogen-progestin combination drugs:* • Rise in blood pressure in susceptible individuals • Premenstrual syndrome • Changes in libido • Changes in appetite • Cystitis-like syndrome • Headache • Nervousness • Fatigue • Backache • Hirsutism • Loss of scalp hair • Erythema multiforma • Erythema nodosum • Hemorrhagic eruption	

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Itching • Dizziness *The following laboratory results may be altered by the use of estrogen-progestin combination drugs:* • Increased sulfobromophthalein retention and other hepatic function tests • Coagulation tests: increase in prothrombin factors VII, VIII, IX, and X • Metyrapone test • Pregnanediol determinations • Thyroid function: increase in PBI, and butanol extractable protein bound iodine and decrease in T3 uptake values	
Medroxyprogesterone acetate (oral; Provera®)	*Warnings:* • Cardiovascular disorders • Stroke • Coronary heart disease • Venous thromboembolism • Malignant neoplasms (breast cancer, endometrial cancer, ovarian cancer) • Dementia • Visual abnormalities *The following adverse reactions have been reported in women taking progestins, including PROVERA tablets, without concomitant estrogens treatment:* • Genitourinary system: Abnormal uterine bleeding (irregular, increase, decrease), change in menstrual flow, breakthrough bleeding, spotting, amenorrhea, changes in cervical erosion and cervical secretions. • Breasts: Breast tenderness, mastodynia or galactorrhea has been reported. • Cardiovascular: Thromboembolic disorders including thrombophlebitis and pulmonary embolism have been reported. • Gastrointestinal: Nausea, cholestatic jaundice. • Skin: Sensitivity reactions consisting of urticaria, pruritus, edema and generalized rash have occurred. Acne, alopecia and hirsutism have been reported. • Eyes: Neuro-ocular lesions, e.g., retinal thrombosis and optic neuritis. • Central nervous system: Mental depression, insomnia, somnolence, dizziness, headache, nervousness.	Provera [package insert]. New York, NY: Pharmacia and Upjohn Company; 2009.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Miscellaneous: Hypersensitivity reactions (e.g., anaphylaxis & anaphylactoid reactions, angioedema), rash (allergic) with and without pruritus, change in weight (increase or decrease), pyrexia, edema/fluid retention, fatigue, decreased glucose tolerance. *The following additional adverse reactions have been reported with estrogen and/or progestin therapy:* • Genitourinary system: Abnormal uterine bleeding/spotting, or flow; breakthrough bleeding; spotting; dysmenorrheal/pelvic pain, increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer. • Breasts: Tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer. • Cardiovascular: Deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure. • Gastrointestinal: Nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis, enlargement of hepatic hemangiomas. • Skin: Chloasma or melasma that may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash. • Eyes: Retinal vascular thrombosis, intolerance to contact lenses. • Central nervous system: Headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia. • Miscellaneous: Increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthalgias; leg cramps; changes in libido; urticaria, angioedema, anaphylactoid/anaplylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.	
Norethisterone [norethindrone] (oral; Aygestin®)	*Warnings:* • Cardiovascular disorders • Visual anomalies *The following adverse reactions have been observed in women taking progestins:* • Breakthrough bleeding • Spotting	Aygestin [package insert]. Sellersville, PA: Teva Pharmaceuticals; 2010.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Change in menstrual flow • Amenorrhea • Edema • Changes in weight (decreases, increases) • Changes in the cervical squamo-columnar junction and cervical secretions • Cholestatic jaundice • Rash (allergic) with and without pruritus • Melasma or chloasma • Clinical depression • Acne • Breast enlargement/tenderness • Headache/migraine • Urticaria • Abnormalities of liver tests (i.e., AST, ALT, Bilirubin) • Decreased HDL cholesterol and increased LDL/HDL ratio • Mood swings • Nausea • Insomnia • Anaphylactic/anaphylactoid reactions • Thrombotic and thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, retinal vascular thrombosis, cerebral thrombosis and embolism) • Optic neuritis (which may lead to partial or complete loss of vision)	
Progesterone (vaginal gel; Crinone®)	*Warnings:* The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). *In one clinical study for assisted reproductive technology, AEs associated with treatment, occurring in 5% or more of women:* • Bloating 7% • Cramps NOS 15% • Pain 8% • Dizziness 5% • Headache 13% • Nausea 7% • Breast Pain 13% • Moniliasis Genital 5% • Vaginal Discharge 7%	Crinone [package insert]. Livingston, NJ: Columbia Laboratories; 2009.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Pruritus Genital 5% *In a second clinical study for assisted reproductive technology (ART), AEs associated with treatment, occurring in ≥5% of women:* • Abdominal Pain 12% • Perineal Pain Female 17% • Headache 17% • Constipation 27% • Diarrhea 8% • Nausea 22% • Vomiting 5% • Arthralgia 8% • Depression 11% • Libido Decreased 10% • Nervousness 16% • Somnolence 27% • Breast Enlargement 40% • Dyspareunia 6% • Nocturia 13% *In three clinical studies for secondary amenorrhea taking (either 4%, 8%) Crinone along with estrogen, AEs associated with treatment, occurring in 5% or more of women:* • Abdominal Pain 5%, 9% • Appetite Increased 5%, 8% • Bloating 13%, 12% • Cramps NOS 19%, 26% • Fatigue 21%, 22% • Headache 19%, 15% • Nausea 8%, 6% • Back Pain 8%, 3% • Myalgia 8%, 0% • Depression 19%, 15% • Emotional Lability 23%, 22% • Sleep Disorder 18%, 18% • Vaginal Discharge 11%, 3% • Upper Respiratory Tract Infection 5%, 8% • Pruitis genital 2%, 6% *Reported in women at a frequency <5% in Crinone ART and secondary*	

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	amenorrhea studies and not listed above include: • Mouth dry • Sweating increased • Abnormal crying • Allergic reaction • Allergy • Appetite decreased • Asthenia • Edema • Face edema • Fever • Hot flushes • Influenza-like symptoms • Water retention • Xerophthalmia • Syncope • Migraine • Tremor • Dyspepsia • Eructation • Flatulence • Gastritis • Toothache • Thirst • Cramps legs • Leg pain • Skeletal pain • Benign cyst • Purpura • Aggressive reactions • Forgetfulness • Insomnia • Anemia • Dysmenorrheal • Premenstrual tension • Vaginal dryness • Infection • Pharyngitis • Sinusitis • Urinary tract infection	

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Asthma • Dyspnea • Hyperventilation • Rhinitis • Acne • Pruritus • Rash • Seborrhea • Skin discoloration • Skin disorder • Urticaria • Cystitis • Dysuria • Micturition frequency • Conjunctivitis	
Progesterone (coil; Progestasert) NOTE: marketing discontinued in US; labels are not available.	See progesterone in general. *Common:* • Abdominal pain (vaginal insert, 12%) • Constipation (vaginal insert, 2% to 3%) • Nausea (vaginal insert; 7% to 8%) • Swollen abdomen (vaginal insert, 4%) • Post-oocyte retrieval (vaginal insert, 25% to 28%) • Fatigue (vaginal insert, 2% to 3%)	Progesterone. In: Micromedex® Healthcare Series. Thomson Reuters (Healthcare) Inc. http://www.thomsonhc.com (accessed March 31, 2012). "Progesterone." In: DrugPoints® System. Thomson Reuters (Healthcare) Inc. http://www.thomsonhc.com (accessed March 31, 2012).
Flurbiprofen (oral; Ansaid®)	*Reported adverse events in patients receiving Ansaid or other NSAIDs* *Warnings and Precautions:* • Cardiovascular thrombotic events, myocardial infarction, and stroke • Hypertension • Congestive heart failure and edema • Gastrointestinal effects, including risk of ulceration, bleeding, and perforation • Renal effects • Advanced renal disease • Anaphylactoid reactions • Skin reactions • Hepatic effects; borderline elevations of liver tests can occur in up to 15% of patients taking NSAIDs including flurbiprofen • Hematological effects	Ansaid [package insert]. New York City, NY: Pharmacia & Upjohn Co.; 2010.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Vision changes (blurred and/pr diminished vision) • Cross reactivity in patients with aspirin-sensitive asthma *Incidence ≥1% from clinical trials:* • Edema • Abdominal pain • Constipation • Diarrhea • Dyspepsia/ heartburn • Elevated liver enzymes • Flatulence • GI bleeding • Nausea • Vomiting • Body weight changes • Headache • Nervousness and other manifestations of CNS stimulation (e.g., anxiety, insomnia, increased reflexes, tremor) • Symptoms associated with CNS inhibition (e.g., amnesia, asthenia, depression, malaise, somnolence) • Rash, • Changes in vision • Dizziness/ vertigo • Tinnitus • Signs and symptoms suggesting urinary tract infection *Incidence <1% from clinical trials, postmarketing surveillance, or literature, with probable causal relationship:* • Anaphylactic reaction • Chills • Fever • Congestive heart failure • Hypertension • Vascular diseases • Vasodilation • Bloody diarrhea • Esophageal disease • Gastric / peptic ulcer disease • Gastritis • Jaundice (cholestatic and noncholestatic)	

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Hematemesis • Hepatitis • Stomatitis / glossitis • Aplastic anemia (including agranulocytosis or pancytopenia) • Decrease in hemoglobin and hematocrit • Ecchymosis / purpura • Eosinophilia • Hemolytic anemia • Iron deficiency anemia • Leucopenia • Thrombocytopenia • Hyperuricemia • Ataxia • Cerebrovascular ischemia • Confusion • Paresthesia • Twitching • Asthma • Epistaxis • Angioedema • Eczema • Exfoliative dermatitis • Photosensitivity • Pruritus • Toxic epidermal necrolysis • Urticaria • Conjunctivitis • Parosmia • Hematuria • Interstitial nephritis • Renal failure *Incidence <1% from clinical trials, postmarketing surveillance, or literature, with causal relationship unknown:* • Angina pectoris • Arrhythmias • Myocardial infarction • Appetite changes • Cholecystitis • Colitis	

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Dry mouth • Exacerbation of inflammatory bowel disease • Periodontal abscess • Small intestine inflammation with loss of blood and protein • Lymphadenopathy • Hyperkalemia • Convulsion • Cerebrovascular accident • Emotional lability • Hypertonia • Meningitis • Myasthenia • Subarachnoid hemorrhage • Bronchitis • Dyspnea • Hyperventilation • Laryngitis • Pulmonary embolism • Pulmonary infarct • Alopecia • Dry skin • Herpes simplex / zoster • Nail disorder • Sweating • Changes in taste • Corneal opacity • Ear disease • Glaucoma • Retinal hemorrhage • Retrobulbar neuritis • Transient hearing loss • Menstrual disturbances • Prostate disease • Vaginal and uterine hemorrhage • Vulvovaginitis	
Meclofenamate sodium (oral; Mecolmen®)	*Warnings:* • Risk of GI ulceration, bleeding and perforation with NSAID therapy *Reported incidence greater than 1%:* • Diarrhea (10% to 33%)	Meclofenamate sodium [package insert]. Morgantown, WV: Mylan Pharmaceuticals; 2006. "[A]dverse reactions were observed in clinical trials and included observations from more than 2,700

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Nausea with or without vomiting (11%) • Other gastrointestinal disorders (10%) • Anorexia • Constipation • Stomatitis • Peptic ulcer • Edema • Urticaria • Pruritus • Tinnitus *Reported incidence between 3% and 9%%:* • Abdominal pain • Pyrosis • Flatulence • Rash • Headache • Dizziness *Reported incidence less than 1%, probably causally related:* • Bleeding and/or perforation with or without obvious ulcer formation • Colitis • Cholestatic jaundice • Renal failure • Neutropenia • Thrombocytopenic purpura • Leucopenia • Agranulocytosis • Hemolytic anemia • Eosinophilia • Decrease in hemoglobin and/or hematocrit • Erythema multiforme • Stevens-Johnson Syndrome • Exfoliative dermatitis • Alteration of liver function tests • Lupus and serum sickness-like symptoms *Reported incidence less than 1%, causal relationship unknown:* • Palpitations • Malaise	patients, 594 of whom were treated for one year and 248 for at least two years." "In approximately 4% of the patients in controlled studies, diarrhea was severe enough to require discontinuation of meclofenamate sodium."

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Fatigue • Paresthesia • Insomnia • Depression • Blurred vision • Taste disturbances • Decreased visual acuity • Temporary loss of vision • Reversible loss of color vision • Retinal changes including macular fibrosis • Macular and perimacular edema • Conjunctivitis • Iritis • Nocturia • Paralytic ileus • Erythema nodosum • Hair loss	
Mefenamic acid (oral; Ponstel®)	*Warnings and precautions:* • Cardiovascular risk, including thrombotic events, hypertension, and congestive heart failure and edema • Gastrointestinal risk *Most frequently reported, occurring in approximately 1-10% of patients:* • Abdominal pain • Constipation • Diarrhea • Dyspepsia • Flatulence • Gross bleeding / perforation • Heartburn • Nausea • GI ulcers (gastric / duodenal) • Vomiting • Abnormal renal function • Anemia • Dizziness • Edema • Elevated liver enzymes • Headaches • Increased bleeding time	Ponstel [package insert]. Atlanta, GA: Shionogi Pharma; 2010.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Pruritus • Rashes • Tinnitus *Additional adverse experiences reported occasionally include:* • Fever • Infection • Sepsis • Congestive heart failure • Hypertension • Tachycardia • Syncope • Dry mouth • Esophagitis • Gastric/peptic ulcers • Gastritis • Gastrointestinal bleeding • Glossitis • Hematemesis • Hepatitis • Jaundice • Ecchymosis • Eosinophilia • Leucopenia • Melena • Purpura • Rectal bleeding • Stomatitis • Thrombocytopenia • Weight changes • Anxiety • Asthenia • Confusion • Depression • Dream abnormalities • Drowsiness • Insomnia • Malaise • Nervousness • Paresthesia	

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Somnolence • Tremors • Vertigo • Asthma • Dyspnea • Alopecia • Photosensitivity • Pruritus • Sweat • Blurred vision • Cystitis • Dysuria • Hematuria • Interstitial nephritis • Pliguria/polyuria • Proteinuria • Renal failure *Other adverse reactions, which occur rarely:* • Anaphylactoid reactions • Appetite changes • Death • Arrhythmia • Hypotension • Myocardial infarction • Palpitations • Vasculitis • Eructation • Liver failure • Pancreatitis • Agranulocytosis • Hemolytic anemia • Aplastic anemia • Lymphadenopathy • Pancytopenia • Hyperglycemia • Convulsions • Coma • Hallucinations • Meningitis	

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Respiratory depression • Pneumonia • Angioedema • Toxic epidermal necrosis • Erythema multiforme • Exfoliative dermatitis • Stevens-Johnson Syndrome • Urticaria • Conjunctivitis • Hearing impairment	
Naproxen (oral; EC-Naprosyn®, Naprosyn®, Anaprox®, Anaprox DS®, Naprosyn®, others)	*Incidence 3-9% of patients in clinical trials with naproxen:* • Heartburn • Abdominal pain • Nausea • Constipation • Headache • Dizziness • Drowsiness • Pruritus • Skin eruptions • Ecchymoses • Tinnitus • Edema • Dyspnea *Incidence <3% of patients in clinical trials with naproxen:* • Diarrhea • Dyspepsia • Stomatitis • Lightheadedness • Vertigo • Sweating • Purpura • Visual disturbances • Hearing disturbances • Palpitations • Thirst *Incidence <1% of patients in clinical trials with naproxen:* • Gastrointestinal bleeding	"Adverse reactions reported in controlled clinical trials in 960 patients treated for rheumatoid arthritis or osteoarthritis are listed [here]. In general, reactions in patients treated chronically were reported 2 to 10 times more frequently than they were in short-term studies in the 962 patients treated for mild to moderate pain or for dysmenorrhea." EC-Naprosyn / Naprosyn / Anaprox / Anaprox DS / Naprosyn [package insert]. Nutley, NJ: Roche Pharmaceuticals; 1999-200X.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Jaundice • Melena • Thrombocytopenia • Agranulocytosis • Inability to concentrate • Skin rashes *Incidence <1% of patients in taking naproxen, from postmarketing reports:* • Anaphylactoid reactions • Angioneurotic edema • Menstrual disorders • Pyrexia (chills and fever) • Congestive heart failure • Vasculitis • Hypertension • Pulmonary edema • Perforation • Hematemesis • Colitis • Exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn's disease) • Nonpeptic gastrointestinal ulceration • Ulcerative stomatitis • Esophagitis, peptic ulceration • Abnormal liver function tests • Hepatitis (some cases have been fatal) • Eosinophilia • Leucopenia • Granulocytopenia • Hemolytic anemia • Aplastic anemia • Hyperglycemia • Hypoglycemia • Depression • Dream abnormalities • Insomnia • Malaise • Myalgia • Muscle weakness	

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Aseptic meningitis • Cognitive dysfunction • Convulsions • Eosinophilic pneumonitis • Asthma • Alopecia • Urticaria • Toxic epidermal necrolysis • Erythema multiforme • Erythema nodosum • Fixed drug eruption • Lichen planus • Pustular reaction • Systemic lupus erythematoses • Bullous reactions, including Stevens-Johnson Syndrome • Photosensitive dermatitis • Photosensitivity reactions, including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa. If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored. • Hearing impairment • Corneal opacity • Papillitis • Retrobulbar optic neuritis • Papilledema • Glomerular nephritis • Hematuria • Hyperkalemia • Interstitial nephritis • Nephrotic Syndrome • Renal disease • Renal failure • Renal papillary necrosis • Raised serum creatinine • Infertility in women	
Cabergoline (oral)	*Incidence during 4-week RCT (% in cabergoline group, % in placebo group):* • Nausea (27, 20) • Constipation (10, 0) • Abdominal pain (5, 5)	Cabergoline [package insert]. Sellersville, PA: Teva Pharmaceuticals; 2011.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Dyspepsia (2, 0) • Vomiting (2, 0) • Headache (26, 25) • Dizziness (15, 5) • Paresthesia (1, 0) • Vertigo (1, 0) • Asthenia (9, 10) • Fatigue (7, 0) • Hot flashes (1, 5) • Somnolence (5, 5) • Depression (3, 5) • Nervousness (2, 0) • Postural hypotension (4, 0) • Breast pain (1, 0) • Dysmenorrhea (1, 0) • Abnormal vision (1, 0) *Incidence during 8-week trial (% in cabergoline group, % in bromocriptine group):* • Nausea (29, 43) • Constipation (7, 9) • Abdominal pain (5, 8) • Dyspepsia (5, 7) • Vomiting (4, 7) • Dry mouth (2, 1) • Diarrhea (2, 3) • Flatulence (2, 1) • Throat irritation (1, 0) • Toothache (1, 0) • Headache (26, 27) • Dizziness (17, 18) • Vertigo (4, 4) • Paresthesia (2, 3) • Asthenia (6, 6) • Fatigue (5, 8) • Syncope (1, 1) • Influenza-like symptoms (1, 0) • Malaise (1, 0) • Periorbital edema (1, 1) • Peripheral edema (1, 1)	

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Depression (3, 2) • Somnolence (2, 2) • Anorexia (1, 1) • Anxiety (1, 1) • Insomnia (1, 1) • Impaired concentration (1, 1) • Nervousness (1, 2) • Hot flashes (3, 1) • Hypotension (1, 2) • Dependent edema (1, 1) • Palpitation (1, 2) • Breast pain (2, 3) • Dysmenorrhea (1, 1) • Acne (1, 0) • Pruritus (1, 1) • Pain (2, 3) • Arthralgia (1, 0) • Rhinitis (1, 4) • Abnormal vision (1, 1) *Reported at an incidence of < 1% in the overall clinical studies:* • Facial edema • Influenza-like symptoms • Malaise • Hypotension • Syncope • Palpitations • Dry mouth • Flatulence • Diarrhea • Anorexia • Weight loss • Weight gain • Somnolence • Nervousness • Paresthesia • Insomnia • Anxiety • Nasal stuffiness • Epistaxis	

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Acne • Pruritus • Abnormal vision • Dysmenorrhea • Increased libido *Postmarketing surveillance data:* • Cardiac valvulopathy • Extracardiac fibrotic reactions • Hypersexuality • Increased libido • Pathological gambling • Cases of alopecia • Aggression and psychotic disorder	
Etamsylate [ethamsylate] (oral) NOTE: not available in US; labels are not available.	*Precautions:* • Patients with asthma, allergies, or a history of allergic-type reactions to medications (potential for allergic phenomena; tablets/ampules contain sodium sulfite) • Patients with or a history of thromboembolism (eg, ischemic stroke, pulmonary embolism, deep-vein thrombosis) • Renal impairment (most of a dose is excreted unchanged) *Adverse reactions:* • Thromboembolic disorder • Rash • Acute intermittent porphyria • Gastrointestinal tract findings: nausea, abdominal discomfort, bitter taste, and other nonspecific gastrointestinal disturbances have been reported occasionally during oral therapy • Backache (causality uncertain) • Headache (causality is questionable)	Ethamsylate. In: Micromedex® Healthcare Series. Thomson Reuters (Healthcare) Inc. http://www.thomsonhc.com (accessed March 31, 2012). DRUGDEX® System. Thomson Reuters (Healthcare) Inc. http://www.thomsonhc.com (accessed March 31, 2012).
Exenatide (injection; Byetta®, others)	Hypoglycemia is a common adverse effect. *Treatment-emergent ARs ≥2% incidence and greater incidence with BYETTA treatment used with metformin and/or a sulfonylurea, excluding hypoglycemia:* • Nausea • Vomiting • Diarrhea	Byetta [package insert]. San Diego, CA: Amylin Pharmaceuticals; 2011.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Feeling jittery • Dizziness • Headache • Dyspepsia • Asthenia • Gastroesophageal reflux disease • Hyperhidrosis *Treatment-emergent ARs ≥2% incidence and greater incidence with BYETTA treatment used with thiazolidinedione, with or without metformin, excluding hypoglycemia:* • Nausea • Vomiting • Dyspepsia • Diarrhea • Gastroesophageal reflux disease *Treatment-emergent ARs ≥2% incidence and greater incidence with BYETTA treatment used with insulin glargine, with or without oral antihyperglycemic medications, excluding hypoglycemia:* • Nausea • Vomiting • Diarrhea • Headache • Constipation • Dyspepsia • Asthenia • Abdominal distension • Decreased appetite • Flatulence • Gastroesophageal reflux disease *Postmarketing experience:* • Injection-site reactions • Generalized pruritus and/or urticaria • Macular or papular rash • Angioedema • Anaphylactic reaction • International normalized ratio (INR) increased with concomitant warfarin use sometimes associated with bleeding	

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Nausea, vomiting, and/or diarrhea resulting in dehydration • Abdominal distension • Abdominal pain • Eructation • Constipation • Flatulence • Acute pancreatitis • Hemorrhagic and necrotizing pancreatitis sometimes resulting in death • Dysgeusia • Somnolence • Altered renal function, including increased serum creatinine • Renal impairment • Worsened chronic renal failure or acute renal failure (sometimes requiring hemodialysis) • Kidney transplant and kidney transplant dysfunction • Alopecia	
Metformin (oral; Glucophage®, others)	*Warning:* • Lactic acidosis (boxed warning) *Most common (>5%) in placebo-controlled study of monotherapy:* • Diarrhea • Nausea/vomiting • Flatulence • Asthenia • Indigestion • Abdominal discomfort • Headache *Also reported (≥1.0% to ≤5%):* • Abnormal stools • Hypoglycemia • Myalgia • Lightheaded • Dyspnea • Nail disorder • Rash • Sweating increased • Taste disorder • Chest discomfort • Chills	Glucophage [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2009.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	• Flu Syndrome • Flushing • Palpitation	
N-acetyl-cysteine	*Warning:* After proper administration of acetylcysteine, an increased volume of liquified bronchial secretions may occur. When cough is inadequate, the open airway must be maintained by mechanical suction if necessary. When there is a mechanical block due to foreign body or local accumulation, the airway should be cleared by endotracheal aspiration, with or without bronchoscopy. Asthmatics under treatment with acetylcysteine should be watched carefully. Most patients with bronchospasm are quickly relieved by the use of a bronchodilator given by nebulization. If bronchospasm progresses, this medication should be discontinued immediately. *Adverse reactions from intravenous include:* • Tachycardia not otherwise specified • Nausea • Vomiting not otherwise specified • Anaphylactoid reaction • Pharyngitis • Rhinorrhea • Rhonchi • Throat tightness • Pruritus • Rash not otherwise specified • Flushing *Adverse reactions from solution include:* • Stomatitis • Nausea • Vomiting • Fever • Rhinorrhea • Drowsiness • Clamminess • Chest tightness • Bronchoconstrictiong • Acquired sensitization to acetylcysteine (rare)	Acetadote [package insert]. Nashville, TN: Cumberland Pharmaceuticals; 2011. Aceytlcysteine solution [package insert]. Lake Forest, IL: Hospira, Inc.; 2004.

Drug (Route; Brand Name)	Adverse Reactions / Effects	Notes and References
	Adverse reactions from other oral preparations (e.g., tablets) are not listed in package inserts. *Adverse reactions reported in postmarketing safety study of IV formulation include:* • Urticaria/facial flushing (6.1%) • Pruritus (4.3%) • Respiratory symptoms (1.9%) • Edema (1.6%) • Hypotension (0.1%) • Anaphylaxis (0.1%)	

Appendix O. Systematic Reviews[a]

Review Title Author, Year	Review Type Intervention	Findings
Efficacy of tranexamic acid in the treatment of idiopathic and non-functional heavy menstrual bleeding: A systematic review. Naoulou et al., 2012[1]	Systematic review of 10 studies (5 double-blind RCTs; 2 RCTs; 1 prospective cohort; 1 comparative; 1 observational study) Tranexamic acid	"Available evidence indicates that tranexamic acid therapy in women with idiopathic menorrhagia resulted in 34–54% reduction in menstrual blood loss. Following tranexamic acid treatment, patient's quality-of-life parameters improved by 46–83%, compared with 15–45% for norethisterone treatment. When compared with placebo, tranexamic acid use significantly decreased the blood loss by 70% in women with menorrhagia secondary to an intrauterine device ($p<0.001$). Limited evidence indicated potential benefit in fibroid patients with menorrhagia. No thromboembolic event was reported in all studies analyzed."
Tranexamic acid therapy for heavy menstrual bleeding. Lumsden and Wedisinghe, 2011[2]	Systematic review Tranexamic acid	"Although several treatment options are available for HMB, tranexamic acid is particularly useful in women who either desire immediate pregnancy or for whom hormonal treatment is inappropriate. Tranexamic acid is a well-tolerated, cost-effective drug that reduces menstrual blood loss in the range of 34-59%. It improves the health-related quality of life in women in HMB."
Effective treatment of heavy and/or prolonged menstrual bleeding without organic cause: pooled analysis of two multinational, randomised, double-blind, placebo-controlled trials of oestradiol valerate and dienogest. Fraser et al., 2011[3]	Pooled analysis of 2 RCTs (421 women in ITT population) Estradiol valerate / dienogest	Mean blood loss reduced in women with heavy and/or prolonged menstrual bleeding, and the effect is seen at the first withdrawal bleed after initiation of treatment. The effect is consistent across a larger and more diverse population of women. "Although not directly comparable, the median decrease in MBL achieved by treatment cycle 7 with E2V/DNG treatment (88%) appears to approach that achieved with the LNG-IUS (median 95% and 96% reduction) over six cycles in two studies that also used the alkaline haematin method to objectively assess blood loss in women with heavy menstrual bleeding."
Cost-effectiveness and quality of life associated with heavy menstrual bleeding among women using the levonorgestrel-releasing intrauterine system. Blumenthal et al., 2011[4]	Review LNG-IUS	"Treating heavy menstrual bleeding with the LNG-IUS was found to be cost-effective in various countries and settings. Moreover, irrespective of the measuring instrument used, health-related quality-of-life outcomes were found to be improved to a degree similar to that achieved with endometrial ablation or hysterectomy. In some cases, the LNG-IUS appeared to be more effective and less costly than the surgical options."
Systematic review highlights difficulty interpreting diverse clinical outcomes in abnormal uterine bleeding trials. Rahn et al., 2011[5]	Systematic review Includes medical and surgical interventions	" Many interventions for abnormal uterine bleeding (AUB) are tested in clinical trials, but the large number and diversity of outcomes reported limit the ability to compare treatments across trials… There is a dearth of standardized outcome measures in AUB that identify symptoms of importance to patients. Further research is required to develop validated measures that capture patient-based outcomes, are responsive to change, yet feasible to use in future trials."

Review Title Author, Year	Review Type Intervention	Findings
Clinical practice guidelines on menorrhagia: management of abnormal uterine bleeding before menopause. Marret et al., 2010[6]	Clinical practice guidelines	"In idiopathic AUB, the first-line treatment is medical, with efficacy ranked as follows: levonorgestrel IUD, tranexamic acid, oral contraceptives, either estrogens and progestins or synthetic progestins only, 21 days a month, or NSAIDs. When hormone treatment is contraindicated or immediate pregnancy is desired, tranexamic acid is indicated. Iron must be included for patients with iron-deficiency anemia. For women who do not wish to become pregnant in the future and who have idiopathic AUB, the long-term efficacy of conservative surgical treatment is greater than that of oral medical treatment. Placement of a levonorgestrel IUD (or administration of tranexamic acid by default) is recommended for women with idiopathic AUB. If this fails, a conservative surgical technique must be proposed…"
Chinese Herbal Medicine for Dysfunctional Uterine Bleeding: a Meta-analysis. Tu et al., 2009[7]	Meta-analysis Chinese herbal medicine (CHM) and conventional Western medicine (CWM)	"Trials of CHM treatments with CWM treatments were compared with CWM treatments alone. Jadad scale and allocation concealment were used to assess the quality of included studies. Four RCTs or quasi-RCTs involving 525 patients were included. The methodological quality was poor in all trials except one trial. No serious adverse events were reported in the included studies. With the lack of trials comparing CHM with no treatment or placebo, it is impossible to accurately evaluate the efficacy of CHM. However, CHM in these studies seem to show an encouraging comparative effectiveness with CWM. More RCTs with a higher quality are required."
The experience of heavy menstrual bleeding: a systematic review and meta-ethnography of qualitative studies. Garside et al., 2008[8]	Systematic review and meta-ethnography	"These provided support for the fourth paper's conceptual framework of a lay model of heavy menstrual bleeding which shows little overlap with the traditional clinical definition. Details of physical, practical and emotional elements of this model were identified. A matrix of uncertainties were identified suggesting reasons why women may or may not seek medical help for heavy menstrual bleeding. Women and healthcare professionals may conspire to privilege blood loss over other symptoms and the disease model of heavy menstrual bleeding is little help to either."
Abnormal uterine bleeding: a review of patient-based outcome measures. Matteson et al., 2009[9]	Systematic review of patient-based outcome measures (983 studies, 80 eligible)	"Fifty different instruments were used to evaluate amount of bleeding, bleeding-related symptoms, or menstrual bleeding-specific quality of life. The quality of each of these instruments was evaluated on eight psychometric properties. The majority of instruments had no documentation of reliability, precision, or feasibility. There was no satisfactory evidence that any one instrument completely addressed all eight psychometric properties."
A systematic review evaluating health-related quality of life, work impairment, and health-care costs and utilization in abnormal uterine bleeding. Liu et al., 2007[10]	Systematic review to evaluate the impact of AUB on health-related quality of life and to quantify the economic burden from a societal perspective	"The prevalence of AUB among women of reproductive age ranged from 10% to 30%. The HRQoL scores from the 36-item Short-Form Health Survey Questionnaire (SF-36) suggested that women with AUB have HRQoL below the 25th percentile of that for the general female population within a similar age range. The conservatively estimated annual direct and indirect economic costs of AUB were approximately $1 billion and $12 billion, respectively. These figures do not account for intangible costs and productivity loss due to presenteeism."

Review Title Author, Year	Review Type Intervention	Findings
Current treatment of dysfunctional uterine bleeding. Bongers et al., 2004[11]	Review	"Antifibrinolytic tranexamic acid is the most effective medical therapy to treat dysfunctional uterine bleeding. In general medical therapy is not as effective as endometrial resection in terms of patient satisfaction and health related quality of life. The levonorgestrel releasing intra uterine device is an effective treatment for dysfunctional uterine bleeding. No difference in quality of life was observed in patients treated with a levonorgestrel releasing intra uterine device as compared to hysterectomy."
Quality of life instruments in studies of menorrhagia: a systematic review. Clark et al., 2002[12]	Systematic review Quality of life instruments	"A total of 19 articles, 8 on instrument development and 11 on application, were included in the review. The generic Short Form 36 Health Survey Questionnaire (SF36) was used in 12/19 (63%) studies. Only two studies developed new specific QoL instruments for menorrhagia but they complied with 7/17 (41%) and 10/17 (59%) of the quality criteria. Quality assessment showed that only 7/19 (37%) studies complied with more than half the criteria for face validity whereas 17/19 (90%) studies complied with more than half of the criteria for measurement properties (P = 0.0001)."
ACOG practice bulletin: management of anovulatory bleeding (2001) American College of Obstetricians and Gynecologists[13]		"The treatment of choice for anovulatory uterine bleeding is medical therapy with oral contraceptives. Cyclic progestins also are effective. (Level A evidence)"
The effectiveness of the levonorgestrel-releasing intrauterine system in menorrhagia: a systematic review. Stewart et al., 2001[14]	Systematic review (5 controlled trials and 5 case series) LNG-IUS	"Small studies of moderate quality indicate the LNG-IUS is an effective treatment for menorrhagia. Costs may be less than for tranexamic acid in primary and secondary care. Although its use may reduce surgical waiting lists, cost effectiveness assessment requires longer follow up."
Thrombotic risks of oral contraceptives. Rott, 2012[15]	Review Contraceptive vaginal ring	"The venous thromboembolism risk for transdermal COCs like vaginal ring (Nuvaring) or patch (Evra) is as high as for COCs of third or fourth generation." "Second-generation COCs should be first choice when prescribing hormonal contraception"
Contraceptive vaginal rings: a review. Brache and Faundes, 2010[16]	Systematic review	"The incidence of estrogen-related adverse events such as breast tenderness, headache and nausea was similar between the NuvaRing and COC users. The only difference… was the higher incidences of loca events such as leucorrhea, vaginitis, vaginal discomfort and ring-related events (foreign body sensation, coital problems, expulsions)." (In Ring users)
Combined hormonal contraception and bone health: a systematic review. Martins et al., 2006[17]	Systematic review (one vaginal ring cohort study) Contraceptive vaginal ring	"…measured changes in BMD among 105 users of a combined CRV (Nuvaring, 15 µg EE/120 µg etongestrel daily)and 39 nonhormonal contraceptive users aged 18-35 years. Over 24 months, BMD at the spine and femoral neck did not change significantly in the ring group but increases in the control group (NuvaRing vs control, p<0.0001). Because differences in BMD between the two groups were within 1 S.D. of each other, the study authors did not consider them to be clinically relevant."

[a] Does not include systematic reviews published by the Cochrane Collaboration or reviews of interventions (e.g., surgical intervention, medical treatments not used in primary care) or populations (e.g., women with bleeding due to fibroids or systemic disease, post-menopausal women, acute bleeding, etc.) outside the scope of this review.

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Appendix P. Ongoing Studies

Study Name Study Status Location Trial Identifier	Inclusion / Exclusion Criteria	Interventions / Groups	Sponsor	Start Date Anticipated Completion Date	Estimated Enrollment
Pretreatment With Norethindrone Acetate Prior to Levonorgestrel IUS Insertion for Heavy Menstrual Bleeding **Currently recruiting** United States NCT01391052	**Inclusion Criteria:** Women aged 18-45 years old with heavy periods US **Exclusion Criteria:** Pregnant Currently using hormonal contraception or hormonal therapy History of pelvic inflammatory disease Infected abortion within the last three months Abnormal or cancerous cells of the cervix or uterus Active infection of genital organs Known or suspected breast cancer Active liver disease or tumors Allergy to levonorgestrel or norethindrone Deep vein thrombosis, pulmonary embolism, or history of arterial thromboembolic disease	**Drug**: Norethindrone acetate (Aygestin) pretreatment 5 mg tablets, three times a day for 21 days for 2 menstrual cycles. **Other**: No pretreatment. LNG-IUS is placed without norethindrone acetate pretreatment.	Scott and White Hospital & Clinic	January 2011 January 2013	80
Mirena Observational Program **Currently recruiting** Kazakhstan NCT00883662	**Inclusion Criteria:** Older than 18 years with previously taken decision of their gynecologist to insert Mirena according to registered indications **Exclusion Criteria:** Contraindications to Mirena insertion, according to approved prescribing information.	**Drug**: Levonorgestrel releasing intrauterine device (Mirena, BAY86-5028)	Bayer	June 2009 April 2014	7500
Multicenter Study to Investigate the Bleeding Profile and the Insertion Easiness in Women Inserted With a Second Consecutive MIRENA for Contraception or	**Inclusion Criteria:** Woman currently using MIRENA for contraception or menorrhagia with duration use between 4 years 3 months and 4 years 9 months and willingness to continue with the method. Normal size uterus at insertion (6-10 cm) Clinically normal cervical smear result within 12 preceding months or at screening. Clinically normal breast examination findings. **Exclusion Criteria:**	**Drug**: Mirena (BAY86-5028) Removal of first MIRENA and insertion of the second MIRENA at entry visit. Removal of MIRENA (in vitro release rate 20 µg/24 h) at year 5 visit. **Drug**: Cytotec, single, sublingual dose of 400 µg, 3	Bayer	October 2006 September 2012	204

Study Name Study Status Location Trial Identifier	Inclusion / Exclusion Criteria	Interventions / Groups	Sponsor	Start Date Anticipated Completion Date	Estimated Enrollment
Menorrhagia **Ongoing but not recruiting** Finland, France, Ireland, Sweden NCT00393198	Menopausal symptoms impairing patient's quality of life or current estrogen therapy for menopausal symptoms. Known or suspected pregnancy. Any distortion of the uterine cavity, including congenital or acquired uterine anomalies and fibroids Current or recurrent pelvic inflammatory disease. Abnormal uterine bleeding of unknown origin. Acute cervicitis or vaginitis not responding to treatment. History of, diagnosed or suspected genital or other malignancy (excluding treated squamous cell carcinoma of the skin), and untreated cervical dysplasia. Any active acute liver disease or liver tumor. **Publications:** Heikinheimo O, Inki P, Kunz M, Parmhed S, Anttila AM, Olsson SE, Hurskainen R, Gemzell-Danielsson K. Double-blind, randomized, placebo-controlled study on the effect of misoprostol on ease of consecutive insertion of the levonorgestrel-releasing intrauterine system. Contraception. 2010 Jun;81(6):481-6. Epub 2010 Mar 1. Gemzell-Danielsson K, Inki P, Boubli L, O'Flynn M, Kunz M, Heikinheimo O. Bleeding pattern and safety of consecutive use of the levonorgestrel-releasing intrauterine system (LNG-IUS)--a multicentre prospective study. Hum Reprod. 2010 Feb;25(2):354-9. Epub 2009 Dec 1.	hours prior to the MIRENA removal and insertion procedure at entry visit **Drug**: Placebo - single, sublingual dose, 3 hours prior to the MIRENA removal and insertion procedure at entry visit			
Evaluation of Whether the Selective Progesterone Receptor Modulator CDB-2914 Can Reduce Bleeding in Premenopausal Women With	**Inclusion Criteria:** Women aged 25-40 years in good health History of abnormal uterine bleeding (anovulatory and ovulatory) documented by menorrhagia impact questionnaire (MIQ) and menstrual calendar Ovulatory women will be defined as those who have menstrual cycles of 24 - 35 days and a progesterone value > 3.0 pg/mL between 5 and 9 days after in-home documentation of an LH surge Anovulatory women will be defined as	**Drug**: CDB-2914	Bayer	November 2011 August 2014	50

Study Name Study Status Location Trial Identifier	Inclusion / Exclusion Criteria	Interventions / Groups	Sponsor	Start Date Anticipated Completion Date	Estimated Enrollment
Abnormal Uterine Bleeding: A Pilot Study **Not yet recruiting** United States NCT01493791	those without an in-house LH surge in whom progesterone values 3 and 4 weeks after menses are < 3.0 ng/mL Hemoglobin > 10 g/dL (for those wishing surgery) Willing and able to comply with study requirements Using mechanical (condoms, diaphragms), sterilization or abstinence methods of contraception for the duration of the study Negative urine pregnancy test BMI less than or equal to 33, if a surgical candidate or less than or equal to 35, if not a surgical candidate. Creatinine less than 1.3 mg/dL Liver function tests within 130 percent of upper limit Women who elect surgery must state that they do not desire further fertility. Endometrial biopsy without endometrial hyperplasia or neoplasia Normal cervical cytology screening within the last 12 months **Exclusion Criteria:** Significant abnormalities in the history, physical or laboratory examination Pregnancy or lactation Use of oral, injectable or inhaled glucocorticoids or megesterol within the last year History of malignancy within the past 5 years Vaginal bleeding in context of anatomic abnormality, endometrial neoplasia or hyperplasia, cervical, vaginal, or vulvar neoplasia or preneoplastic pathology Use of estrogen or progesterone-containing compounds Current use of agents known to induce hepatic P450 enzymes Use of imidazoles Current use of GnRH analogs or other compounds that affect menstrual cyclicity Use of herbal medication having estrogenic or antiestrogenic effects within the past 3 months Untreated cervical dysplasia Need for interval use of narcotics Abnormal adnexal/ovarian mass Contradiction to anesthesia, for women planning surgery				

Study Name Study Status Location Trial Identifier	Inclusion / Exclusion Criteria	Interventions / Groups	Sponsor	Start Date Anticipated Completion Date	Estimated Enrollment
	Leiomyomata, polyps or other anatomic causes of vaginal bleeding Previous participation in the study Thrombocytopenia defined as platelets < 150,000 **Publications:** Batista MC, Cartledge TP, Zellmer AW, Merino MJ, Axiotis C, Loriaux DL, Nieman LK. Delayed endometrial maturation induced by daily administration of the antiprogestin RU 486: a potential new contraceptive strategy. Am J Obstet Gynecol. 1992 Jul;167(1):60-5. Bushnell DM, Martin ML, Moore KA, Richter HE, Rubin A, Patrick DL. Menorrhagia Impact Questionnaire: assessing the influence of heavy menstrual bleeding on quality of life. Curr Med Res Opin. 2010 Dec;26(12):2745-55. Epub 2010 Nov 3. Cadepond F, Ulmann A, Baulieu EE. RU486 (mifepristone): mechanisms of action and clinical uses. Annu Rev Med. 1997;48:129-56. Review.				

DNG = dienogest; EV = estradiol valerate; GnRH: gonadotropin-releasing hormone; LNG-IUS = levonorgestrel-releasing intrauterine system; TXA = tranexamic acid. MPA: medroxyprogesterone; DMPA: depot medroxyprogesterone