Treatment options for women with heavy menstrual bleeding: A comprehensive systematic review, network meta-analysis, and health economic assessment

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Document version overview table

Version	Date	Changes
v1.0	9th May 2023	First version of the protocol
v2.0	21st May 2024	Added or amended items: 1. Master search strategy for Medline 2. PROSPERO registration records for the specific research questions 3. Change to order of outcomes of interest to reflect women's preferences (safety and quality of life added to main outcomes) 4. Updated reference list 5. Change of author (addition of Lily Nicholson)

1. Introduction

Heavy menstrual bleeding (HMB) affects one in four women of reproductive age leading to significant impairment of their quality of life (1). Although the cause of HMB remains unknown in most affected women, about 50000 women in England and Wales seek specialist treatment at secondary care services annually (2), constituting approximately 20% of referrals to the National Health Service (NHS) gynaecology services (3). Around 28,000 women eventually require surgery to manage their HMB (4). As well as surgery, several medical treatment options are offered for HMB (e.g. progestogen-releasing Intra-Uterine Systems (IUS), contraceptive pills, Danazol, Ulipristal acetate, nonsteroidal anti-inflammatory drugs, anti-fibrinolytic agents, gonadotropin-releasing hormone agonists). Because HMB is a chronic condition that affects the health, wellbeing and productivity of otherwise healthy women at varied life stages (adolescents, pre-pregnancy, perimenopause, it is important to consider women's evolving health needs and life stage to maximise the benefit and uptake of the varied HMB treatment options. For example, women with HMB and uterine desiring pregnancy may opt for fertility-sparing treatments like hysteroscopic fibroid resection and magnetic resonance-guided transcutaneous focussed ultrasound fibroid ablation, in preference to more radical treatments such as a hysterectomy or uterine artery embolization (5).

Reliable evidence synthesis is key to counselling affected women and informing their decision-making and treatment selection (5). Existing systematic reviews have tended to offer generic assimilation of data, and/or overviews of aggregate data from meta-analyses with head-to-head comparisons of individual treatments (6, 7), potentially failing to make best use of the wealth of existing data with poor translation into clinical practice (8). Importantly, women's voices have been missing from these prior attempts to synthesize data.

Currently, NICE recommends the use of levonorgestrel-releasing intrauterine system (IUS) as the first line treatment option, reserving surgical options until medical treatments have failed or are undesirable (7). However, a pairwise Cochrane meta-analysis (25 Randomised Clinical Trials (RCTs), 2511 women) suggested that compared to surgery, women using IUS have less control of HMB, lower satisfaction, and more adverse events (mastalgia, weight gain, and acne) (9). Recent studies suggested reduced effectiveness for IUS in particular subgroups (e.g., women with uterine fibroids and adenomyosis) (10).

Recent rapid progress in surgical technology (e.g., novel endometrial ablation technology (11) and total laparoscopic hysterectomy (12)) could facilitate long term, reliable and safe treatments for certain women's subgroups (e.g. peri-menopause) with persistent HMB at a lower cost to the NHS (13, 14). Similarly, several new pharmacological treatments are now offered to women with HMB and fibroids (e.g., Elagolix and Ulipristal acetate) which may offer more benefits, though their adoption is varied across NHS services (15). With these new treatments being introduced into clinical practice, remaining uncertainties in existing recommendations, and the lack of consideration of the views and treatment preferences of women with HMB(16, 17), there is now a need clear, comprehensive and succinct evidence synthesis, to update and re-examine the evidence to identify the most effective, acceptable and cost-effective treatments to be offered to affected women across NHS services.

Aim and objectives

Aim

- To provide relevant, comprehensive, and up-to-date evidence on the clinical and cost effectiveness of available treatment options for women with HMB
- To better inform clinical recommendations and guidelines to improve outcomes for women overall, and within specific population subgroups.

Objectives

1. To identify all relevant randomised trials that evaluated any treatment option for HMB through comprehensive literature searches.
2. To evaluate the relative effectiveness and safety of all available treatment options for HMB overall and within key subgroups based on factors relating to the characteristics of affected women and their preferred treatment options.
4. To evaluate the cost-effectiveness and utility of identified treatment options for improving the quality adjusted life years of women with HMB within the National Health Service.
5. To produce a decision aid toolkit and overall ranking of evaluated treatments for their effectiveness and safety within specific population subgroups.

2. Methods

Clinical effectiveness and safety

We will conduct a suite of systematic reviews of **randomised trials** with pairwise (direct evidence) meta-analyses, and network meta-analysis (mix of direct and indirect evidence) evaluating any treatment options for HMB compared to placebo, no intervention, or other treatment options.

We define our **population** as any person of a reproductive age affected by HMB from any cause or due to unknown cause.

The **interventions** will include the following categories:

a) Any hormonal treatment (including combined contraceptives, progesterone-only pills, combined vaginal ring, synthetic steroids, intra-uterine hormone releasing systems).
b) Any pharmacological non-hormonal treatment (including antifibrinolytics or haemostatic agents, anti-inflammatory agents, progesterone receptor modulator agents)
c) Surgical treatment options (including open (abdominal), vaginal or laparoscopic hysterectomy, endometrial ablation, hysteroscopic resection of fibroid, myomectomy, uterine artery embolization.

Based on the relevant clinical practice guidelines, Cochrane systematic reviews, and core outcomes sets (18-20) we identified key **outcomes of importance** to stakeholders.
We aim to evaluate the intervention effect primarily on the **change in menstrual blood loss** (using Pictorial blood loss assessment chart scores, or the Alkaline-Haematin method), quality of life (general and disease-specific), and treatment safety (e.g., surgical

complications or thrombosis while using contraceptive treatments). The other outcomes of interest are the chance of post-treatment amenorrhoea, dysmenorrhoea, changes in haemoglobin, treatment satisfaction (assessed using dichotomous or Likert scale questionnaires) and need for retreatment.

2.1. Study selection

We will perform systematic searches of the literature using the following steps:

a) **Electronic databases** (MEDLINE, EMBASE, CENTRAL): using a multi-stage search strategy combining MeSH terms and keywords using the Boolean operators AND/OR. No search filters or language restrictions will be employed (See **Search strategy).**
b) **International clinical trials registries** (Clinicaltrials.gov, EU-CTR, ISRCTN): to identify any ongoing and/or recently completed trials.
c) **Grey Literature**: We will perform complementary searches in Google Scholar and Scopus to screen for potentially relevant citations in the grey literature.
d) **Hand searching**: Clinical Practice Guidelines on the management of HMB, relevant Cochrane reviews, and bibliographies of relevant articles to identify any missed citations.

To reduce duplication of efforts, our searches will aim to supplement eligible trials identified for inclusion in previous evidence synthesis (6, 7). Consequently, our literature search will cover a period from **1 January 2019 and will be updated quarterly until** 6 months before the end of the project (**June 2024**). We will exclude quasi and non-randomised studies, reviews, and animal studies. Articles will not be restricted by language.

2.2. Data collection

We will screen relevant citations using the COVIDENCE systematic review software, using Cochrane methodology to select trials. We will map out all the selection steps through a study flow diagram. For all retrieved trials, we will record whether they match our eligibility criteria and the reasons for exclusion. Two of the review authors will extract data, including from multiple intervention arms and subgroups from each study using a bespoke form.

Before embarking on data synthesis, collected data will be checked for accuracy and credibility, where necessary, we will contact trial investigators throughout, to facilitate thorough data checking and querying and to ensure that data on all outcomes and subgroups of importance are collected for each trial, even when not directly available from trial reports. This approach has facilitated rapid evaluation of the effects of various treatments, overall and in relevant subgroups (21-23).

2.3. Risk of bias assessment

We will assess the risk of bias for each study to be included in meta-analyses, using guidance outlined in the Cochrane Handbook (21) and the Cochrane Risk of Bias 2 tool, for the specific domains of random sequence generation, allocation concealment, blinding of participants and personnel, blinding (low risk if at least double blinded), incomplete outcome data (low risk of bias if less than 10% missing data), selective reporting, and other sources

of bias, such as conflict of interest and method of measuring blood loss (objective, subjective or not specified)(21). Each domain will be assigned a judgment relating to the risk of bias for that study: low risk, high risk, and unclear, except for blinding where an intermediate risk will be assigned if at least the outcome assessor was blinded.
We will assess the trustworthiness of identified studies using the Cochrane Pregnancy and Childbirth Group screening tool (22) and Trustworthiness in RAndomised Controlled Trials (TRACT) tool (23). Where measures of quality are unclear, we will work proactively with relevant trialists to gain additional information and refine the risk of bias assessment of included studies (24).

2.4. Pair-wise meta-analysis

In the first instance, we will perform a suite of pairwise meta-analyses to understand the nature of the direct evidence (See **References**

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3. Search strategy

Master search strategy for Medline (via Ovid)

Item	Term
1	menorrhagia/
2	menorrhag$.tw.
3	(menstrua$ adj5 (bleed$ or blood)).tw.
4	(heavy adj5 menstrua$).tw.
5	(dysfunctional adj5 uter$).tw.

6	hypermenorrh$.tw.
7	heavy menstrual bleeding.ab,ti.
8	heavy period$.ab,ti.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	randomized controlled trial.pt.
11	controlled clinical trial.pt.
12	randomized.ab.
13	placebo.tw. 244794
14	clinical trials as topic.sh.
15	randomly.ab.
16	trial.ti.
17	crossover.tw.
18	cross-over.tw.
19	cross over.tw.
20	17 or 18 or 19
21	10 or 11 or 12 or 13 or 14 or 15 or 16 or 20
22	9 and 21
23	exp animals/ not humans.sh.
24	22 not 23
25	limit 24 to yr="2019 -Current"

Supplementary Protocols). The primary analysis will combine the effect estimates across trials using the fixed-effect model to estimate the overall risk of an event on treatment compared with control. Since only randomised controlled trials are eligible, confounding factors may be assumed to be balanced across arms, so that we may synthesise data appropriately using raw count data (dichotomous outcomes) or using raw means and standard deviations (continuous outcomes).

We aim to limit missing data as far as possible through collaboration with participating trialists and will carry out analyses on an intention-to-treat basis, i.e., we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether they received the allocated intervention. For included studies, we will note levels of attrition and if necessary, conduct sensitivity analysis. For our main analysis, we will analyse the available data without imputation. However, if there is substantial missing data for an analysis of specific clinical interest, we may conduct sensitivity analyses where data are imputed using methods described in the Cochrane Handbook (21).

The main outcome, improvement in menstrual bleeding, has been reported using a variety of measures and at varying timepoints. We will aim to collect, or request directly from trialists, relevant data using a consistent definition across trials, likely to be the mean (with standard deviation), at protocol-defined timepoints. If this is not possible, disparate continuous outcome measures would be pooled after applying standardization, and pairwise results presented overall and by trial subgroups defined by the underlying outcome measure.

For continuous outcome measures, we will report the posterior mean difference with 95% confidence intervals. Where the target parameter is the effect of treatment on the change in continuous variable between baseline and follow-up, we will check whether the trial methodology correctly accounted for the within patient correlation between baseline and follow-up estimates. If not, we will apply an approximate correction using methods described in the Cochrane Handbook (21). For dichotomous outcomes, we will extract (or request) numbers of participants who did and did not experience each outcome according to intervention group, overall and in subgroups defined by trial characteristics or patient characteristics at the time of randomisation. We will compare the statistical fit of models that fit log-odds ratios and log relative risk estimates for the primary outcomes. The best-fitting effect measures for the primary outcomes will be used for all primary and secondary outcomes. If there is no statistical reason to prefer one over the other, we will use estimates of relative risk for ease of interpretation.

3.1. Subgroup and sensitivity analyses

We will work to refine and prioritise comparison subgroups, most relevant for individual pairwise comparisons, with relevant stakeholders and lay patient representatives. Where possible, we will explore the varied treatment effect across the following subgroup categories:

- Treatment characteristics: class (medical vs surgical), type (e.g., hormonal vs non-hormonal), mode of delivery (oral, vaginal, injection), dose.
- Participant characteristics: age group (adolescent, pre-pregnancy, perimenopausal), prior treatment (naïve, pre-treated), desire for pregnancy, uterine anomaly (e.g., fibroids, adenomyosis).

If we identify substantial heterogeneity in the pairwise analysis of the main outcome, we will investigate it using trial-level subgroup analyses and sensitivity analyses. For patient-level subgroups, we will test for differences in effect (covariate interactions) within each trial and then pool these across trials, and a related the “within-trial framework” (25, 26) to estimate subgroup-specific pooled treatment effects.

Sensitivity analyses will be conducted according to the quality of the studies, trial publication date (before and after 2000), trial size (excluding small studies, in recognition of the greater likelihood for small studies than large or multi-centre studies to suffer publication bias) and whether an objective method of outcome assessment was employed. On the quality assessment, studies will be labelled to have a low, medium, or high risk of bias as per the Cochrane Risk of Bias 2 tool (27). We consider protocol publication in advance of the results to be an unsuitable criterion for sensitivity analyses because protocol publication only became widespread in recent years (post 2000). Sensitivity analyses will be restricted to the main outcomes.

3.2. Network meta-analysis

If sufficient data are available, and assuming pairwise analyses do not suggest that trial estimates should not be combined (e.g., very large unexplained heterogeneity; violation of transitivity assumption between treatment comparisons), then we will carry out a network meta-analysis by fitting consistency random-effects models for the primary outcome assuming the same between-study variance.

For dichotomous outcomes, where relative risks are estimated, the model will be based upon log-ratio estimates and standard errors. For continuous measures, the model will be based upon mean differences and standard errors. Between-studies heterogeneity will be assessed by consideration of the between-study variance parameter. We will also fit inconsistency models and determine sources of inconsistency within the network (if present) using loop splitting.

As a sensitivity analysis, we will also fit a model allowing a different between-study variance parameter per contrast. For all secondary outcomes including side effects we will fit the same model that was chosen for the primary outcomes. For continuous variables we will fit linear mixed effect regression models as described above.

If there is evidence that the inconsistency model has better predictive properties, then we will report this and carefully consider whether it is appropriate to conduct a network meta-analysis (bearing in mind that chance results are possible given the number of secondary outcomes). If poor fit is detected in both the consistency and inconsistency models, then we will assess the fit of a model that allows the between studies variance to be different for each contrast. In addition, individual contributions to the residual deviance from each study will be examined to identify outliers. All analyses will be performed using Stata v.18 (StataCorp).

3.3. Presentation of the findings

In addition to pooled effect estimates we will calculate the probability, conditional on the model and the parameterisation for vague prior beliefs, that each treatment is the most clinically effective. We will also calculate the probability that each treatment holds each rank

and the cumulative probabilities that each treatment is of a specific rank or higher for all ranks where rank indexes from one to the number of treatments. Between studies heterogeneity will be assessed by consideration of the between study variance parameter and assessment of model fit of the fixed and random effects models. We will use the GRADE (28, 29) or alternative approach (30) to rate the certainty of the evidence for the overall effect of across the included trials for the primary outcome.

Health economics

3.4. Economic perspective and data collection

We will evaluate the costs and health benefits associated with using each treatment option and their combinations in the NHS by reporting on the quality-adjusted life years (QALYs) reflecting a cost-utility analysis. We will report on the net monetary benefit (NMB) for a range of cost-effectiveness thresholds for each treatment. Uncertainty will be explored using deterministic and probabilistic sensitivity analysis as per established methodology for time-horizon, cost perspective, calculating QALYs and discounting.

The choice for the most effective treatment for HMB should incorporate both the patient preference (e.g., medical vs surgical), risk profile, and potential cost implication in the health care sector. For example, undergoing a total hysterectomy would offer the maximum effectiveness in stopping HMB, however, this option won't be favoured by nulliparous younger women planning for pregnancy and would certainly come with increased health cost in the short term.

Furthermore, the potential for cost saving that might be implied by some short-term medical treatment (e.g., hormone-releasing intrauterine systems) might be offset by additional costs of repeated failed treatment, prolonged morbidity and adverse impact on quality-of-life measures in the long-term.

A model-based economic analysis is ideally suited to collate the appropriate evidence from a range of sources and explore alternative scenarios and the uncertainty surrounding a range of possible results including subgroup analysis. Thus, if available data allow, the economic evaluation will be based on an outcome of cost per QALY and/or cost per morbidity free survival post-event (this latter is an outcome we have used in our previous analysis due to the paucity of quality-of-life data).

We will also include analyses based on a range of other outcomes including treatment satisfaction, adverse events, days missed of work/school and other outcomes identified as important by women with evidence in the literature. The analysis will adopt a health service perspective. Therefore, data collection required for the model-based economic evaluation will include:

- Total treatment costs (based on dose, route and regimen of administration, other resource use and costs associated with reducing HMB including staff involved in the intervention and duration of their involvement).
- Specialist equipment used in the procedure (e.g., total laparoscopic hysterectomy).
- Knock-on costs associated with additional and failed treatments including length of inpatient stay, level of care received during inpatient stay and readmission to hospital.
- Satisfaction and quality of life outcomes associated with HMB.

Once the clinical evidence has been synthesised to provide the relative effectiveness and side-effects with the ranking of each treatment for resolution of HMB, the relevant studies will be examined for their data on costs and resource use. We will also search the wider literature for costs of event data. These data will be subjected to relevant quality criteria including GRADE and guidance set out by NICE Decision Support Unit and The Professional Society for Health Economics and Outcomes Research (ISPOR). Additional cost data will be available from other sources such as the National Schedule for Reference Costs and the British National Formulary. If necessary, primary cost and resource data will be collected from University College London Hospitals to complete any gaps in the information required for the modelling process.

The evidence found in the systematic reviews will provide most of the parameters required to carry out the model-based economic evaluations of evaluated treatment options. Additional searches as part of a wider pragmatic review will be undertaken to help structure and populate the decision model. We will consult relevant stakeholders to identify the model questions. These questions may relate to preference-based health related quality of life associated with HMB or analogous conditions; costs and duration associated with inpatient stay or side-effects of the treatments or morbidity as a result of treatment for HMB. Information to answer these questions will be provided by focused searching of appropriate databases, including reference cost databases, statistical sources and other sources of relevant information.

3.5. Economic model and analysis

We will develop a decision model using data from the systematic review considering the structure of women's health services in the NHS. The model will be developed in consensus with relevant stakeholders (e.g., clinicians and patient representatives) to reflect the current patient journey to access treatments. We will search the literature for evidence of existing model-based analyses for this clinical area and use these to inform our model structure as far as appropriate. Given the relatively short-term impact of the intervention and treatment, the most appropriate model structure will be a simple decision tree, although we will explore other model structures including Markov models.

We will leverage data from our evidence synthesis to construct the model based on the cost per QALY. However, experience from similar research suggests that appropriate data on QALY outcomes are likely to be limited. As such, we will not attempt to model a whole lifetime and we will look for data and information that are related specifically to post-treatment outcomes with no specific time limit. Where we are not able to find suitable parameters from the published sources to populate the model, we will make assumptions based on expert opinion and after the consultation with relevant stakeholders. A modelling framework is ideally suited to demonstrate and explore the importance of the inherent uncertainty: we will conduct and report the results of deterministic and probabilistic sensitivity analysis. An incremental approach will be adopted with a focus on additional costs and gain in benefits associated with a move away from the current treatment to resolve HMB to an alternative treatment. Net-monetary benefit (QALYS multiplied by a cost effectiveness threshold) will be reported to allow comparisons across a range of treatment options. Costs and benefits will be discounted in line with NICE guidance.

3.6. Presentation of economic results and sensitivity analysis:

The results of these economic analyses will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties for a range of cost-effectiveness thresholds. Deterministic sensitivity analyses will be used to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used and to consider the broader issue of the generalisability of the results.

3.7. Discrete choice experiment

We aim to produce a health economic model that reflects the true health needs of women with HMB and incorporates their treatment preferences to inform health policy. Given the evolving health needs and priorities of women across different life stages, it is not clear if QALYs would sufficiently capture the outcomes of interest for women being treated for HMB.

As a result, we will first conduct a few focus groups (10-20 lay patient representatives) to determine the key outcomes of interest and treatment attributes for women with HMB. These focus groups will be run in partnership with our PPI-co applicants to ensure inclusive and representative sampling for a range of different ages, ethnicities and conditions.

We will then use the treatment rankings from our evidence synthesis and the patient input from the focus groups to construct treatment choice sets within a Discrete Choice Experiment that would help us to model the treatment preferences of women with HMB. We aim to recruit 200-500 lay patient representatives (depending on the number of evaluated choices) who will be recruited over social media and key contracts of our lay collaborators (Katie's Team and the Co-Production Collective). We will internally pilot the Discrete Choice Experiment within our lay collaborators' membership to ensure the choice sets are understood by a lay audience and hold face and content validity.
Participants will be asked to choose from treatment choice sets (each including scenario A or B) and select their preferred option. This task will be repeated by varying the values for the key outcomes of interests. Participants' responses will be analysed using methods of increasing complexity to determine which variables best explain treatment preferences. We will seek input from our lay patient representatives to assess the feasibility of including a cost variable that would allow us to calculate willingness to pay for different treatment outcomes. The results and final weightings of the Discrete Choice Experiment will be then incorporated to inform the design and decision of the planned model.

4. Project management

The project will be managed within the framework of the MRC Clinical Trials Unit at UCL, which will provide access to the required infrastructure, quality management, and data hosting services. The project Co-CIs (BHA and CV) will hold joint responsibility for overseeing the conduct and delivery of the project outputs as per the scheduled activities. The Co-CIs will chair regular team meetings (in person and virtual) and submit regular progress reports to the funder. A dedicated research fellow will be responsible for day-to-day project activities working under the supervision of (ER) and (BHA).

A Project Steering Committee with an independent chair and lay patient representatives (selected from the membership of Katie's Team, the Co-Production Collective, and other

relevant charities and lay service user groups) will be constituted to govern and monitor the project conduct. The Committee will have a specific advisory role to ensure sufficient representation of lay service users and other relevant stakeholders as per the planned PPIE strategy.

We will adopt an Agile Project Management Methodology to drive efficiency and minimize tasks interdependency. Where possible we will use cloud-based software (e.g., COVIDENCE) and share regular task e-updates to set short and long-term delivery targets for team members. E-communication software (e.g., Trello) will be used to share precise asynchronous updates and tasks with team members. Risk analysis and contingency planning will be performed by the Co-CIs quarterly in view of reported progress and in consultation with the Project Steering Committee. Regular progress reports capturing key performance indicators, contingency planning, and forecasted activities will be submitted to the funder at set milestones.

5. Ethics

The planned evidence synthesis is exempt from NHS REC approval as a secondary research project. We plan to involve volunteering lay patient representatives who are not under active treatment. We will not collect personal identifiable data, only summary statistics for the meta-analyses, however, we will seek ethics approval from local ethics committee where relevant (e.g. qualitative survey, discrete choice experiment). We will ensure all research activities are in line with the principles of GDPR, GCP and the Department of Health Research Framework.

6. Dissemination plan

The research question is inherently of high impact given the expressed institutional interest in this health topic from NICE, Royal College of Obstetricians and Gynaecologists, the Government initiative for women's health, several charities and lay service user groups. We plan to disseminate the project outputs across the following mediums:

Conferences: The findings will be disseminated among health professionals via oral and poster presentations at the annual conferences of the Royal College of Obstetricians and Gynaecologists, Royal College of General Physicians, British Fertility Society, British Society for Gynaecological Endoscopy, British Society for Paediatric and Adolescent Gynaecology, The European Society of Human Reproduction and Embryology, European board & college of obstetrics and gynaecology, and the International Federation of Gynecology and Obstetrics (FIGO) conference. We aim also to present at lay conferences dedicated for women's health in the UK and abroad to raise awareness on the issue of HMB and available treatment options.

Peer-reviewed publications: We aim to publish in high impact peer-reviewed journals and an HTA monograph detailing the effectiveness, cost-effectiveness and side-effect profile of

each HMB treatment option. We will disseminate the completed paper to the Department of Health, the NICE guideline development writing committee, the Scientific Advisory Committees of the relevant Royal Colleges and professional societies (e.g., British Fertility Society and the British Society for Gynaecological Endoscopy).

Protocol registration: The master research protocol will be registered prospectively with OSF and protocols for individual clinical questions with PROSPERO. We will also publish the master protocol under Open Access policy in a peer-reviewed journal.

Guidelines: We will communicate our findings with NICE to inform further updates of their HMB guideline (7). We aim to produce a decision toolkit and evidence-based rank-o-gram to aid health professionals and patients in choosing the most appropriate treatment options. Where relevant, we will work with relevant professional societies (e.g., British Fertility Society and The British Society for Paediatric and Adolescent Gynaecology) to aid the production of relevant evidence-based guidelines (e.g., management of fibroids, and HMB in adolescents).

Other copyright: We aim to produce a decision toolkit and evidence-based rank-o-gram to aid both health professionals and patients in choosing the most appropriate treatment options. We will make this toolkit freely available online under creative commons license.

Cochrane reviews: We will continue our collaboration with the Cochrane Gynaecology and Fertility Group to maximise impact and ensure continued knowledge generation beyond the lifetime of this proposal. We will share data summaries to facilitate the update of existing reviews and the commissioning of new reviews where needed.

Media outputs: We will produce lay media outputs to engage the wider community focusing on patients and lay service users such as lay press releases, blog posts, Tweets, short videos, and infographics.

7. Timelines

We forecast a total project duration of 18 months to execute the following steps:

Activity	Time
• Research fellow is appointed, the project master protocol is finalised and uploaded to OSF. • First suits of protocols for individual research questions registered on PROSPERO. • The literature search is completed, and the findings are migrated to COVIDENCE database	June – August 2023
• Completion of data extraction/collection and study risk of bias assessment. • Correspondence with primary trials authors for additional outcomes and subgroups information. • Health economic modelling and literature retrieval initiated.	July 2023 – May 2024
• Data cleaning and credibility check. • Initiate statistical analysis. • Health economic data extraction completed. • Focus groups and Discrete Choice Experiment underway.	February – June 2024

• Statistical analysis finalised, and the final economic modelling completed.	June – October 2024
• Write up and dissemination	September – December 2024

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9. Search strategy

Master search strategy for Medline (via Ovid)

Item	Term
1	menorrhagia/
2	menorrhag$.tw.
3	(menstrua$ adj5 (bleed$ or blood)).tw.
4	(heavy adj5 menstrua$).tw.
5	(dysfunctional adj5 uter$).tw.
6	hypermenorrh$.tw.
7	heavy menstrual bleeding.ab,ti.
8	heavy period$.ab,ti.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	randomized controlled trial.pt.
11	controlled clinical trial.pt.
12	randomized.ab.
13	placebo.tw. 244794
14	clinical trials as topic.sh.
15	randomly.ab.

16 trial.ti.
17 crossover.tw.
18 cross-over.tw.
19 cross over.tw.
20 17 or 18 or 19
21 10 or 11 or 12 or 13 or 14 or 15 or 16 or 20
22 9 and 21
23 exp animals/ not humans.sh.
24 22 not 23
25 limit 24 to yr="2019 -Current"

10. Supplementary Protocols

Supplementary protocol 1

Effect of medical treatments for heavy menstrual bleeding due to uterine fibroids: a systematic review, pairwise and network meta-analysis of aggregate data

Lily Nicholson, Ewelina Rogozinska, Claire Vale, David Fisher, Bassel Al Wattar

Citation

Lily Nicholson, Ewelina Rogozinska, Claire Vale, David Fisher, Bassel Al Wattar. Effect of medical treatments for heavy menstrual bleeding due to uterine fibroids: a systematic review, pairwise and network meta-analysis of aggregate data. **PROSPERO 2023 CRD42023468055**

Review question [1 change]

1. What is the efficacy and safety of medical treatment options for heavy menstrual bleeding in women with uterine fibroids?
2. Does the effect differ due to differences in type of treatments (e.g. hormonal, non-hormonal), composition (monotherapy vs. combined treatment), and dose?
3. Does the effect vary between subgroups of women (e.g. women with larger UF ≥3cm vs women with smaller UF <3cm diameter)?

Searches [2 changes]

We will systematically search the following literature databases:

a) MEDLINE (via Ovid)

b) EMBASE (via Ovid)

c) Cochrane Central Register of Controlled Trials (CENTRAL)

In addition, we will search:

a) **International clinical trials registries** (ClinicalTrials.gov, EU-CTR, ISRCTN): to identify any ongoing and/or recently completed trials.

b) **Grey Literature**: We will perform complementary searches in Google Scholar and Scopus to screen for potentially relevant citations in the grey literature.

c) **Hand searching**: Clinical Practice Guidelines on the management of HMB, relevant Cochrane reviews, and bibliographies of relevant articles to identify any missed citations

In order to eliminate duplication of efforts, streamline the extraction of relevant data and maximise the use of published evidence for the studies published before 2019 we will use the summaries available from the previous evidence synthesis (Clinical Practice Guidelines and Cochrane Reviews on HMB).

Consequently, our literature search will cover a period from 1 January 2019 and will be updated quarterly until 30 June 2024.

The following keywords and MeSH terms describing the condition: "menorrhagia", “heavy menstrual bleeding”, "heavy period", "heavy menstruation", "hypermenorrhagia", and "heavy menstruation", were combined using Boolean operators with the Cochrane recommended filter for randomised controlled trials to identify relevant trials. The search was limited to studies conducted with human participants published after 2019. The search was reviewed using the PRESS 2015 checklist.

Types of study to be included

Any type of randomised controlled trial

Condition or domain being studied [1 change]

Menorrhagia, or heavy menstrual bleeding defined as menstrual blood loss of >80 ml and/or a duration of >7 days

Participants/population

Individuals diagnosed with heavy menstrual bleeding linked to uterine fibroids whose intent is to preserve their fertility

Intervention(s), exposure(s) [1 change]

Any medical therapy: non-hormonal (e.g. antifibrinolytics or haemostatic agents, anti-inflammatory agents, progesterone receptor modulator agents) or hormonal (e.g. combined contraceptives, progesterone-only pills, combined vaginal ring, synthetic steroids, intra-uterine hormone releasing systems).

Surgical interventions are considered as part of a separate protocol (CRD42024519622) and will not be included in this review.

Comparator(s)/control [1 change]

Standard care or placebo, or any other medical therapy (non-hormonal or hormonal).

Context

Any setting

Main outcome(s) [2 changes]

Efficacy

• Change in menstrual blood loss, assessed using pictorial blood loss assessment chart (PBAC) scores, the alkaline-haemitin method or any other validated method

• General and disease specific quality of life (using any validated questionnaires)

Safety outcomes

• Any adverse events

Measures of effect

For dichotomous outcomes, we will estimate risk ratios with 95% confidence intervals.
For continuous outcomes, mean difference or standardised mean difference (for quality of life measures) with 95% confidence intervals.

Additional outcome(s) [2 changes]

• Post-treatment amenorrhoea
• Changes in haemoglobin level
• Dysmenorrhoea (using any validated questionnaires)
• Satisfaction
• Need for retreatment

Measures of effect

For dichotomous outcomes, we will estimate risk ratios with 95% confidence intervals.
For continuous outcomes, mean difference or standardised mean difference (for quality of life measures) with 95% confidence intervals.

Data extraction (selection and coding) [2 changes]

We will screen relevant citations using the COVIDENCE systematic review software, using Cochrane methodology to select trials. We will map out all the selection steps through a study flow diagram. For all retrieved trials, we will record whether they match our eligibility criteria and the reasons for exclusion. Two of the review authors will extract data, including from multiple intervention arms and subgroups from each study using a bespoke form and upload data onto COVIDENCE database.

Following a collaborative approach to meta-analysis, we will maintain open communication with trial investigators throughout, to facilitate thorough data checking and querying and to ensure that data on all outcomes and subgroups of importance are collected for each trial, even when not directly available from trial reports.

Study characteristics

x Publication details (full text or not; year; journal)
x Country
x Accrual dates
x Study design features
x Funding
x Clinical trial registration details and ethics approval

Population characteristics

x Age
x Ethnicity
x Characteristics of heavy period
x Characteristics of uterine anomaly (volume, type)
x Prior treatments if any
x Desire for pregnancy if specified
x Other relevant medical conditions (e.g. anaemia or its indicator [haemoglobin level])

Treatment characteristics
x Type (e.g. hormonal, none-hormonal)
x Composition (monotherapy or combination with other treatments)
x Mode of delivery
x Specific preparation type
x Dose

Outcomes
x Menstrual blood loss
x Quality of life (using any validated scale)
x Adverse events
x Post-treatment amenorrhea
x Haemoglobin
x Dysmenorrhea (using any validated Pain scale)
x Satisfaction
x Need for retreatment

Risk of bias (quality) assessment [1 change]
The Risk of Bias tool (RoB2) for randomised trials will be used to assess the quality of all included trials.
Research integrity will also be assessed using a modified version of the TRACT checklist and the Cochrane Pregnancy and Childbirth Trustworthiness Screening Tool (CPC-TST).

Strategy for data synthesis [1 change]
Characteristics of trials, and of patients recruited to the trials, will be summarised in descriptive tables.

We will compare all individual treatments or classes of treatment versus usual care or placebo in a series of linked pairwise meta-analysis comparisons. The primary analyses will be based on inverse-variance weighted meta-analyses of overall and subgroup effects using a fixed effects approach. We will report precise p values and will not use a threshold for statistical significance. We will quantify inconsistency in effects between trial heterogeneity using I^2 statistics and estimate statistical heterogeneity using a Cochran's Q test.

Where meta-analysis of treatment effect estimates is not possible, for example, if an outcome has been treated differently across trials (e.g. a continuous outcome has been dichotomized in some studies) or analysed using different methods, we will apply an alternative method to synthesise and present findings where possible and appropriate (McKenzie JE, Brennan SE. Chapter 12: Synthesizing and presenting findings using other methods. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook). We will also tabulate the results and report them in full.

If sufficient data are available, and assuming pairwise analyses do not suggest that trial estimates should not be combined (e.g., very large unexplained heterogeneity), then we will carry out a network meta-analysis, by fitting consistency random-effects models for the primary outcome assuming the same between-study variance.

Analysis of subgroups or subsets [1 change]

As well as comparing the effects of treatments overall, providing sufficient data are available, we will also assess the treatment effects between groups of trials defined by :

1. Type of intervention (e.g., hormonal, non-hormonal),
2. Composition of intervention (monotherapy vs. combined treatment)
3. Dose

and using methods described by Fisher et al (BMJ 2017;356:j573), between groups of participants defined by:

1. Age group /life stage (<20; 20-40; >40)
2. Ethnicity (White, Black, Asian)
3. Prior treatment (naïve, pre-treated)
4. Fibroid size (≥3 cm, <3cm)

Pooled effect estimates for each subgroup of interest, consistent with the pooled interaction, will be estimated using methods that avoid aggregation bias (Godolphin et al, Research Synthesis Methods 2022). NB Planned subgroup categorise may be combined to achieve groups of a reasonable size. All p-values will be two-sided.

Contact details for further information

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Organisational affiliation of the review

Meta-Analysis Group, MRC Clinical Trials Unit at UCL
https://www.ucl.ac.uk/comprehensive-clinical-trials-unit/research/evie-research-group

Review team members and their organisational affiliations [1 change]

Ms Lily Nicholson. Meta-Analysis Group, MRC Clinical Trials Unit at UCL
Dr Ewelina Rogozinska. Meta-Analysis Group, MRC Clinical Trials Unit at UCL
Dr Claire Vale. Meta-Analysis Group, MRC Clinical Trials Unit at UCL
Mr David Fisher. Meta-Analysis Group, MRC Clinical Trials Unit at UCL
Dr Bassel Al Wattar. Comprehensive Clinical Trials Unit at UCL

Collaborators

Professor Jayne Tierney. Meta-Analysis Group, MRC Clinical Trials Unit at UCL
Professor Khalid S. Kahan. Department of Preventive Medicine and Public Health, University of Granada
Professor Davor Jurkovic. Women's Health Department, University College London Hospitals
Mrs Ngawai Moss. Katie's Team, Queen Mary University of London
Mrs Niccola Hutchinson-Pascal. Co-production Collective, UCL

Type and method of review

Intervention, Meta-analysis, Network meta-analysis, Systematic review

Anticipated or actual start date

05 June 2023

Anticipated completion date

29 November 2024

Funding sources/sponsors

The National Institute for Health Research and the UK Medical Research Council (https://mrc.ukri.org/)

Grant number(s)

State the funder, grant or award number and the date of award

NIHR153187; MRC grant number: MC_UU_00004/06

Conflicts of interest [1 change]

Language

English

Country

England

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Combined Modality Therapy; Female; Humans; Leiomyoma; Menorrhagia

Date of registration in PROSPERO

03 October 2023

Date of first submission

29 September 2023

Stage of review at time of this submission [1 change]

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	Yes	No
Data analysis	No	No

Revision note

We have refined for precision the text in the fields describing research questions, type of interventions, and strategy for data synthesis - in the latter one mainly by adding a paragraph on how we plan to handle synthesis when meta-analysis won't be possible. Following the consultation with the group of individuals with lived experience of the condition, we have reordered the outcomes by moving quality of life and safety to the main outcomes and moving post-treatment amenorrhea to secondary ones. Finally, we have added a new review member Ms Nicholson.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions
03 October 2023
13 March 2024

Supplementary protocol 2

Effect of surgical and non-surgical procedures for heavy menstrual bleeding due to uterine fibroids: a systematic review, pairwise and network meta-analysis of aggregate data

Lily Nicholson, Ewelina Rogozinska, Claire Vale, David Fisher, Bassel Al Wattar

Citation
Lily Nicholson, Ewelina Rogozinska, Claire Vale, David Fisher, Bassel Al Wattar. Effect of surgical and non-surgical procedures for heavy menstrual bleeding due to uterine fibroids: a systematic review, pairwise and network meta-analysis of aggregate data. **PROSPERO 2024 CRD42024519622**

Review question
1. What is the efficacy and safety of surgical or non-surgical procedures for women with heavy menstrual bleeding due to uterine fibroids.
2. Does the effect differ due to differences in type of procedure used (e.g. laparoscopic vs open, surgical vs non-surgical)?
3. Does the effect vary between subgroups of women (e.g. women with larger UF ≥3cm vs women with smaller UF <3cm diameter)?

Searches
We will systematically search the following literature databases:
a) MEDLINE (via Ovid)
b) EMBASE (via Ovid)
c) Cochrane Central Register of Controlled Trials (CENTRAL)
In addition, we will search:
a) International clinical trials registries (ClinicalTrials.gov, EU-CTR, ISRCTN): to identify any ongoing and/or recently completed trials.
b) Grey Literature: We will perform complementary searches in Google Scholar and Scopus to screen for potentially relevant citations in the grey literature.
c) Hand searching: Clinical Practice Guidelines on the management of HMB, relevant Cochrane reviews, and bibliographies of relevant articles to identify any missed citations

In order to eliminate duplication of efforts, streamline the extraction of relevant data and maximise the use of published evidence for the studies published before 2019 we will use the summaries available from the previous evidence synthesis (Clinical Practice Guidelines and Cochrane Reviews on HMB). Consequently, our literature search will cover a period from 1 January 2019 and will be updated bi-annually until 30 June 2024.

The following keywords and MeSH terms describing the condition: "menorrhagia", “heavy menstrual bleeding”, "heavy period", "heavy menstruation", "hypermenorrhagia", and "heavy menstruation", were combined using Boolean operators with the Cochrane recommended filter for randomised controlled trials to identify relevant trials. The search was limited to studies conducted with human participants published after 2019. The search was reviewed using the PRESS 2015 checklist.

Types of study to be included
Any type of randomised controlled trial

Condition or domain being studied
Menorrhagia, or heavy menstrual bleeding (typically defined as menstrual blood loss of >80ml and/or a duration of >7 days)

Participants/population
Individuals diagnosed with heavy menstrual bleeding linked to uterine fibroids.
Intervention(s), exposure(s)
Any surgical or non-surgical procedure (e.g. open (abdominal), vaginal or laparoscopic hysterectomy, endometrial ablation, hysteroscopic resection of fibroid, myomectomy, uterine artery embolization). Medical treatments for heavy periods associated with uterine fibroids are considered in a separate protocol.

Comparator(s)/control
Any other medical, surgical or non-surgical treatments, or no treatment

Context
Any setting

Main outcome(s)
Efficacy outcomes
• Change in menstrual blood loss, assessed using pictorial blood loss assessment chart (PBAC) scores, the alkaline-haemitin method or any other validated method
• General and disease specific quality of life (using any validated questionnaires)
Safety outcomes
• Adverse events, including surgical complication rates

Measures of effect

For dichotomous outcomes, we will estimate risk ratios with 95% confidence intervals.

For continuous outcomes, mean difference or standardised mean difference (for quality of life measures) with 95% confidence intervals.

Additional outcome(s)

• Post-treatment amenorrhoea
• Changes in haemoglobin level
• Dysmenorrhoea
• Satisfaction
• Need for retreatment

Measures of effect

For dichotomous outcomes, we will estimate risk ratios with 95% confidence intervals.

For continuous outcomes, mean difference or standardised mean difference (for quality of life measures) with 95% confidence intervals.

Data extraction (selection and coding)

We will screen relevant citations using the COVIDENCE systematic review software, using Cochrane methodology to select trials. We will map out all the selection steps through a study flow diagram. For all retrieved trials, we will record whether they match our eligibility criteria and the reasons for exclusion. Two of the review authors will extract data, including from multiple intervention arms and subgroups from each study using a bespoke form and upload data onto COVIDENCE database.

Following a collaborative approach to meta-analysis, we will maintain open communication with trial investigators throughout, to facilitate thorough data checking and querying and to ensure that data on all outcomes and subgroups of importance are collected for each trial, even when not directly available from trial reports.

Study characteristics:

x Publication details (full text or not; year; journal)
x Country
x Accrual dates
x Study design features
x Funding
x Clinical trial registration details and ethics approval

Population characteristics

x Age
x Ethnicity
x Characteristics of heavy period

x Characteristics of uterine anomaly (volume, type) x Prior treatments if any
x Desire for pregnancy if specified
x Other relevant medical conditions (e.g. anaemia or its indicator [haemoglobin level])

Treatment characteristics
x Type (e.g. surgical, non-surgical procedures, hormonal, non-hormonal)
x Composition (monotherapy or combination with other treatments)
x Mode of delivery (for hormonal and non-hormonal comparators)
x Specific preparation type (for hormonal and non-hormonal comparators)
x Dose (for hormonal and non-hormonal comparators)

Outcomes
x Menstrual blood loss
x Quality of life (using any validated scale)
x Adverse events
x Post-treatment amenorrhea
x Haemoglobin
x Dysmenorrhea (using any validated pain scale)
x Satisfaction
x Need for retreatment

Risk of bias (quality) assessment
The Risk of Bias tool (RoB2) for randomised trials will be used to assess quality of all included trials. Research integrity will also be assessed using a modified version of the TRACT checklist and the Cochrane Pregnancy and Childbirth Trustworthiness Screening Tool (CPC-TST).

Strategy for data synthesis
Characteristics of trials, and of patients recruited to the trials, will be summarised in descriptive tables.

We will compare all individual procedural interventions (or class of interventions) versus active comparator or no treatment in a series of linked pairwise meta-analysis comparisons. The primary analyses will be based on inverse-variance weighted meta-analyses of overall and subgroup effects using a fixed effects approach. We will report precise p values and will not use a threshold for statistical significance. We will quantify inconsistency in effects between trials heterogeneity using I^2 statistics and estimate statistical heterogeneity using a Cochran's Q test.

Where meta-analysis of treatment effect estimates is not possible, for example, if an outcome has been treated differently across trials (e.g. a continuous outcome has been dichotomized in some studies) or analysed using different methods, we will apply an alternative method to synthesise and present findings where possible and appropriate (McKenzie JE, Brennan SE. Chapter 12:

Synthesizing and presenting findings using other methods. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook). We will also tabulate the results and report them in full.

If sufficient data are available, and assuming pairwise analyses do not suggest that trial estimates should not be combined (e.g., very large unexplained heterogeneity), then we will carry out a network meta-analysis, by fitting consistency random-effects models for the primary outcome assuming the same between-study variance.

Analysis of subgroups or subsets

As well as comparing the effects of treatments overall, providing sufficient data are available, we will also assess the treatment effects between groups of trials defined by type of procedure (e.g. surgery vs non-surgery, open surgery vs laparoscopic surgery, any surgical or non-surgical procedure vs medical).

We will also use methods described by Fisher et al (BMJ 2017;356:j573), to compare the effects of treatment between groups of participants defined by:

1. Age group /life stage (<20; 20-40; >40)
2. Ethnicity (White, Black, Asian)
3. Prior treatment (naïve, pre-treated)
4. Fibroid size (≥3 cm, <3cm)

Pooled effect estimates for each subgroup of interest, consistent with the pooled interaction, will be estimated using methods that avoid aggregation bias (Godolphin et al, Research Synthesis Methods 2022). NB Planned subgroup categorise may be combined to achieve groups of a reasonable size. All p-values will be two-sided.

Contact details for further information

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Organisational affiliation of the review

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https://www.ucl.ac.uk/comprehensive-clinical-trials-unit/research/evie-research-group

Review team members and their organisational affiliations

Ms Lily Nicholson. Meta-Analysis Group, MRC Clinical Trials Unit at UCL
Dr Ewelina Rogozinska. Meta-Analysis Group, MRC Clinical Trials Unit at UCL
Dr Claire Vale. Meta-Analysis Group, MRC Clinical Trials Unit at UCL

Mr David Fisher. Meta-Analysis Group, MRC Clinical Trials Unit at UCL
Dr Bassel Al Wattar. Comprehensive Clinical Trials Unit at UCL

Collaborators

Professor Jayne Tierney. Meta-Analysis Group, MRC Clinical Trials Unit at UCL
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Professor Davor Jurkovic. Women's Health Department, University College London Hospitals
Mrs Ngawai Moss. Katie's Team, Queen Mary University of London
Mrs Niccola Hutchinson-Pascal. Co-production Collective, UCL

Type and method of review

Intervention, Meta-analysis, Network meta-analysis, Systematic review

Anticipated or actual start date

05 June 2023

Anticipated completion date

29 November 2024

Funding sources/sponsors

The National Institute for Health Research and the UK Medical Research Council (https://mrc.ukri.org/)
Grant number(s)
State the funder, grant or award number and the date of award
NIHR153187; MRC grant number: MC_UU_00004/06

Conflicts of interest

Language

English

Country

England

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

11 March 2024

Date of first submission

11 March 2024

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

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Versions

11 March 2024

Supplementary protocol 3

Effect of medical treatments for heavy menstrual bleeding: a systematic review, pairwise and network meta-analysis of aggregate data

Lily Nicholson, Ewelina Rogozinska, Claire Vale, David Fisher, Bassel Al Wattar

Citation
Lily Nicholson, Ewelina Rogozinska, Claire Vale, David Fisher, Bassel Al Wattar. Effect of medical treatments for heavy menstrual bleeding: a systematic review, pairwise and network meta-analysis of aggregate data. **PROSPERO 2024 CRD42024520558**

Review question

1. What is the efficacy and safety of medical treatment options for women with heavy menstrual bleeding?
2. Does the effect differ due to type of intervention (e.g. hormonal, non-hormonal), composition (monotherapy vs. combined treatment), and dose?
3. Does the effect vary between subgroups of women (e.g. older vs younger women; those previously treated or treatment naive)?

Searches

We will systematically search the following literature databases:
a) MEDLINE (via Ovid)
b) EMBASE (via Ovid)
c) Cochrane Central Register of Controlled Trials (CENTRAL)

In addition, we will search:
d) International clinical trials registries (ClinicalTrials.gov, EU-CTR, ISRCTN): to identify any ongoing and/or recently completed trials.
e) Grey Literature: We will perform complementary searches in Google Scholar and Scopus to screen for potentially relevant citations in the grey literature.
f) Hand searching: Clinical Practice Guidelines on the management of HMB, relevant Cochrane reviews, and bibliographies of relevant articles to identify any missed citations

In order to eliminate duplication of efforts, streamline the extraction of relevant data and maximise the use of published evidence for the studies published before 2019 we will use the summaries available from the previous evidence synthesis (Clinical Practice Guidelines and Cochrane Reviews on HMB). Consequently, our literature search will cover a period from 1 January 2019 and will be updated bi-annually until 30 June 2024.

The following keywords and MeSH terms describing the condition: "menorrhagia", “heavy menstrual bleeding”, "heavy period", "heavy menstruation", "hypermenorrhagia", and "heavy menstruation", were combined using Boolean operators with the Cochrane recommended filter for randomised controlled trials to identify relevant trials. The search was limited to studies conducted with human participants published after 2019. The search was reviewed using the PRESS 2015 checklist.

Types of study to be included

Randomised controlled trials only.

Condition or domain being studied

Menorrhagia, or heavy menstrual bleeding defined as menstrual blood loss of >80ml and/or a duration of >7 days.

Participants/population

Individuals diagnosed with heavy menstrual bleeding not linked to a diagnosis of uterine fibroids.

Intervention(s), exposure(s)

Any medical therapy: non-hormonal (e.g. antifibrinolytics or haemostatic agents, anti-inflammatory agents, progesterone receptor modulator agents) or hormonal (e.g. combined contraceptives, progesterone-only pills, combined vaginal ring, synthetic steroids, intra-uterine hormone releasing systems).

Surgical interventions are considered as part of a separate protocol (registration in process) and will not be included in this review.

Comparator(s)/control

Standard care or placebo, or any other medical therapy (non-hormonal or hormonal).

Context

Any setting.

Main outcome(s)

Efficacy outcomes

• Change in menstrual blood loss, assessed using pictorial blood loss assessment chart (PBAC) scores, the alkaline-haemitin method or any other validated method

• General and disease specific quality of life (using any validated questionnaires)

Safety outcomes

• Adverse events

Measures of effect

For dichotomous outcomes, we will estimate risk ratios with 95% confidence intervals.

For continuous outcomes, mean difference or standardised mean difference (for quality of life measures) with 95% confidence intervals.

Additional outcome(s)

• Post-treatment amenorrhoea
• Changes in haemoglobin level
• Dysmenorrhoea
• Satisfaction
• Need for retreatment

Measures of effect

For dichotomous outcomes, we will estimate risk ratios with 95% confidence intervals.

For continuous outcomes, mean difference or standardised mean difference (for quality of life measures) with 95% confidence intervals.

Data extraction (selection and coding)

We will screen relevant citations using the COVIDENCE systematic review software, using Cochrane methodology to select trials. We will map out all the selection steps through a study flow diagram. For all retrieved trials, we will record whether they match our eligibility criteria and the reasons for exclusion. Two of the review authors will extract data, including from multiple intervention arms and subgroups from each study using a bespoke form and upload data onto COVIDENCE database. Following a collaborative approach to meta-analysis, we will maintain open communication with trial investigators throughout, to facilitate thorough data checking and querying and to ensure that data on all outcomes and subgroups of importance are collected for each trial, even when not directly available from trial reports.

Study characteristics:

x Publication details (full text or not; year; journal)
x Country
x Accrual dates
x Study design features
x Funding
x Clinical trial registration details and ethics approval

Population characteristics:

x Age
x Ethnicity
x Characteristics of heavy period
x Characteristics of uterine anomaly (volume, type) x Prior treatments if any

x Desire for pregnancy if specified
x Other relevant medical conditions (e.g. anaemia or its indicator [haemoglobin level])

Treatment characteristics:
x Type (e.g. hormonal, none-hormonal)
x Composition (monotherapy or combination with other treatments)
x Mode of delivery
x Specific preparation type
x Dose

Outcomes
x Menstrual blood loss
x Quality of life (using any validated scale)
x Adverse events
x Post-treatment amenorrhea
x Haemoglobin
x Dysmenorrhea (using any validated pain scale)
x Satisfaction
x Need for retreatment

Risk of bias (quality) assessment
The Risk of Bias tool (RoB2) for randomised trials will be used to assess quality of all included trials. Research integrity will also be assessed using a modified version of the TRACT checklist and the Cochrane Pregnancy and Childbirth Trustworthiness Screening Tool (CPC-TST).

Strategy for data synthesis
Characteristics of trials, and of patients recruited to the trials, will be summarised in descriptive tables.

We will compare all individual treatments or classes of treatment versus usual care or placebo in a series of linked pairwise meta-analysis comparisons. The primary analyses will be based on inverse-variance weighted meta-analyses of overall and subgroup effects using a fixed effects approach. We will report precise p values and will not use a threshold for statistical significance. We will quantify inconsistency in effects between trials heterogeneity using I^2 statistics and estimate statistical heterogeneity using a Cochran's Q test.

Where meta-analysis of treatment effect estimates is not possible, for example, if an outcome has been treated differently across trials (e.g. a continuous outcome has been dichotomized in some studies) or analysed using different methods, we will apply an alternative method to synthesise and present findings where possible and appropriate (McKenzie JE, Brennan SE. Chapter 12: Synthesizing and presenting findings using other methods. In: Higgins JPT, Thomas J, Chandler J,

Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook). We will also tabulate the results and report them in full.

If sufficient data are available, and assuming pairwise analyses do not suggest that trial estimates should not be combined (e.g., very large unexplained heterogeneity), then we will carry out a network meta-analysis, by fitting consistency random-effects models for the primary outcome assuming the same between-study variance.

Analysis of subgroups or subsets

As well as comparing the effects of treatments overall, providing sufficient data are available, we will also assess the treatment effects between groups of trials defined by :

1. Type of intervention (e.g., hormonal, non-hormonal)
2. Composition of intervention (monotherapy vs. combined treatment)
3. Dose

and using methods described by Fisher et al (BMJ 2017;356:j573), between groups of participants defined by:

1. Age group /life stage (<20; 20-40; >40)
2. Ethnicity (White, Black, Asian)
3. Prior treatment (naïve, pre-treated)

Pooled effect estimates for each subgroup of interest, consistent with the pooled interaction, will be estimated using methods that avoid aggregation bias (Godolphin et al, Research Synthesis Methods 2022). NB Planned subgroup categorise may be combined to achieve groups of a reasonable size. All p-values will be two-sided.

Contact details for further information

Lily Nicholson
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Organisational affiliation of the review

Meta-Analysis Group, MRC Clinical Trials Unit at UCL https://www.ucl.ac.uk/comprehensive-clinical-trials-unit/research/evie-research-group

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Anticipated completion date

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Funding sources/sponsors

The National Institute for Health Research and the UK Medical Research Council (https://mrc.ukri.org/)

Grant number(s)

State the funder, grant or award number and the date of award

NIHR153187; MRC grant number: MC_UU_00004/06

Conflicts of interest

Language

English

Country

England

Stage of review

Review Ongoing

Subject index terms status

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Subject index terms

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Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

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Versions

11 March 2024

Supplementary protocol 4

Effect of surgical and non-surgical procedures for heavy menstrual bleeding: a systematic review, pairwise and network meta-analysis of aggregate data

Lily Nicholson, Ewelina Rogozinska, Claire Vale, David Fisher, Bassel Al Wattar

Citation

Lily Nicholson, Ewelina Rogozinska, Claire Vale, David Fisher, Bassel Al Wattar. Effect of surgical and non-surgical procedures for heavy menstrual bleeding: a systematic review, pairwise and network meta-analysis of aggregate data. **PROSPERO 2024 CRD42024520634**

Review question

1. What is the efficacy and safety of medical treatment options for women with heavy menstrual bleeding?
2. Does the effect differ due to differences in type of procedure used (e.g. laparoscopic vs open, surgical vs non-surgical)?
3. Does the effect vary between subgroups of women (e.g. older vs younger women; those previously treated or treatment naive)?

Searches

We will systematically search the following literature databases:

a) MEDLINE (via Ovid)
b) EMBASE (via Ovid)
c) Cochrane Central Register of Controlled Trials (CENTRAL)

In addition, we will search:

d) International clinical trials registries (ClinicalTrials.gov, EU-CTR, ISRCTN): to identify any ongoing and/or recently completed trials.
e) Grey Literature: We will perform complementary searches in Google Scholar and Scopus to screen for potentially relevant citations in the grey literature.
f) Hand searching: Clinical Practice Guidelines on the management of HMB, relevant Cochrane reviews, and bibliographies of relevant articles to identify any missed citations

In order to eliminate duplication of efforts, streamline the extraction of relevant data and maximise the use of published evidence for the studies published before 2019 we will use the summaries available from the previous evidence synthesis (Clinical Practice Guidelines and Cochrane Reviews on HMB). Consequently, our literature search will cover a period from 1 January 2019 and will be updated bi-annually until 30 June 2024.

The following keywords and MeSH terms describing the condition: "menorrhagia", “heavy menstrual bleeding”, "heavy period", "heavy menstruation", "hypermenorrhagia", and "heavy menstruation", were combined using Boolean operators with the Cochrane recommended filter for randomised controlled trials to identify relevant trials. The search was limited to studies conducted with human participants published after 2019. The search was reviewed using the PRESS 2015 checklist.

Types of study to be included

Randomised controlled trials only.

Condition or domain being studied

Menorrhagia, or heavy menstrual bleeding defined as menstrual blood loss of >80ml and/or a duration of >7 days.

Participants/population

Individuals diagnosed with heavy menstrual bleeding not linked to a diagnosis of uterine fibroids.

Intervention(s), exposure(s)

Any surgical treatment (including open (abdominal), vaginal or laparoscopic hysterectomy, endometrial ablation, uterine artery embolization).

Medical treatments for heavy periods are considered in a separate protocol (registration in progress) and will not be included in this review.

Comparator(s)/control

Any other medical, surgical or non-surgical treatments, or no treatment.

Context

Any setting

Main outcome(s)

Efficacy outcomes

• Change in menstrual blood loss, assessed using pictorial blood loss assessment chart (PBAC) scores, the alkaline-haematin method or any other validated method

• General and disease specific quality of life (using any validated questionnaires)

Safety outcomes

• Adverse events, including surgical complication rates

Measures of effect

For dichotomous outcomes, we will estimate risk ratios with 95% confidence intervals.

For continuous outcomes, mean difference or standardised mean difference (for quality of life measures) with 95% confidence intervals.

Additional outcome(s)

• Post-treatment amenorrhoea
• Changes in haemoglobin level
• Dysmenorrhoea
• Satisfaction
• Need for retreatment

Measures of effect

For dichotomous outcomes, we will estimate risk ratios with 95% confidence intervals.
For continuous outcomes, mean difference or standardised mean difference (for quality-of-life measures) with 95% confidence intervals.

Data extraction (selection and coding)

We will screen relevant citations using the COVIDENCE systematic review software, using Cochrane methodology to select trials. We will map out all the selection steps through a study flow diagram. For all retrieved trials, we will record whether they match our eligibility criteria and the reasons for exclusion. Two of the review authors will extract data, including from multiple intervention arms and subgroups from each study using a bespoke form and upload data onto COVIDENCE database. Following a collaborative approach to meta-analysis, we will maintain open communication with trial investigators throughout, to facilitate thorough data checking and querying and to ensure that data on all outcomes and subgroups of importance are collected for each trial, even when not directly available from trial reports.

Study characteristics:

x Publication details (full text or not; year; journal)
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x Study design features
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Population characteristics

x Age
x Ethnicity
x Characteristics of heavy period
x Characteristics of uterine anomaly (volume, type) x Prior treatments if any
x Desire for pregnancy if specified
x Other relevant medical conditions (e.g. anaemia or its indicator [haemoglobin level])

Treatment characteristics

x Type (e.g. surgical, non-surgical procedures, hormonal, non-hormonal)
x Composition (monotherapy or combination with other treatments)
x Mode of delivery (for hormonal and non-hormonal comparators)
x Specific preparation type (for hormonal and non-hormonal comparators)
x Dose (for hormonal and non-hormonal comparators)

Outcomes

x Menstrual blood loss
x Quality of life (using any validated scale)
x Adverse events
x Post-treatment amenorrhea
x Haemoglobin
x Dysmenorrhea (using any validated pain scale)
x Satisfaction
x Need for retreatment

Risk of bias (quality) assessment

The Risk of Bias tool (RoB2) for randomised trials will be used to assess quality of all included trials. Research integrity will also be assessed using a modified version of the TRACT checklist and the Cochrane Pregnancy and Childbirth Trustworthiness Screening Tool (CPC-TST).

Strategy for data synthesis

Characteristics of trials, and of patients recruited to the trials, will be summarised in descriptive tables.

We will compare all individual procedural treatments (or class of interventions) versus active comparator or no treatment in a series of linked pairwise meta-analysis comparisons. The primary analyses will be based on inverse-variance weighted meta-analyses of overall and subgroup effects using a fixed effects approach. We will report precise p values and will not use a threshold for statistical significance. We will quantify inconsistency in effects between trials heterogeneity using I^2 statistics and estimate statistical heterogeneity using a Cochran's Q test.

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If sufficient data are available, and assuming pairwise analyses do not suggest that trial estimates should not be combined (e.g., very large unexplained heterogeneity), then we will carry out a network meta-analysis, by fitting consistency random-effects models for the primary outcome assuming the same between-study variance.

Analysis of subgroups or subsets

As well as comparing the effects of treatments overall, providing sufficient data are available, we will also assess the treatment effects between groups of trials defined by type of procedure (e.g. surgery vs non-surgery, open surgery vs laparoscopic surgery, any surgical or non-surgical procedure vs medical).

We will also use methods described by Fisher et al (BMJ 2017;356:j573), to compare the effects of treatment between groups of participants defined by:

1. Age group /life stage (<20; 20-40; >40)
2. Ethnicity (White, Black, Asian)
3. Prior treatment (naïve, pre-treated)

Pooled effect estimates for each subgroup of interest, consistent with the pooled interaction, will be estimated using methods that avoid aggregation bias (Godolphin et al, Research Synthesis Methods 2022). NB Planned subgroup categorise may be combined to achieve groups of a reasonable size. All p-values will be two-sided.

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Stage of review
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Formal screening of search results against eligibility criteria	Yes	Yes
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