Cochrane Library

Cochrane Database of Systematic Reviews

Interventions for heavy menstrual bleeding; overview of Cochrane reviews and network meta-analysis (Review)

Bofill Rodriguez M, Dias S, Jordan V, Lethaby A, Lensen SF, Wise MR, Wilkinson J, Brown J, Farquhar C

Bofill Rodriguez M, Dias S, Jordan V, Lethaby A, Lensen SF, Wise MR, Wilkinson J, Brown J, Farquhar C.
Interventions for heavy menstrual bleeding; overview of Cochrane reviews and network meta-analysis.
Cochrane Database of Systematic Reviews 2022, Issue 5. Art. No.: CD013180.
DOI: 10.1002/14651858.CD013180.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Overview of Reviews]

Interventions for heavy menstrual bleeding; overview of Cochrane reviews and network meta-analysis

Magdalena Bofill Rodriguez[1], Sofia Dias[2], Vanessa Jordan[3], Anne Lethaby[4], Sarah F Lensen[5], Michelle R Wise[1], Jack Wilkinson[6], Julie Brown[7], Cindy Farquhar[3]

[1]Department of Obstetrics and Gynaecology, The University of Auckland, Auckland, New Zealand. [2]Centre for Reviews and Dissemination, University of York, York, UK. [3]Department of Obstetrics and Gynaecology, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, New Zealand. [4]Department of Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand. [5]Department of Obstetrics and Gynaecology, University of Melbourne, Melbourne, Australia. [6]Centre for Biostatistics, School of Health Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre (MAHSC), University of Manchester, Manchester, UK. [7]Covidence, Melbourne, Australia

Contact: Magdalena Bofill Rodriguez, m.bofill@auckland.ac.nz.

Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: Edited (no change to conclusions), published in Issue 2, 2023.

Citation: Bofill Rodriguez M, Dias S, Jordan V, Lethaby A, Lensen SF, Wise MR, Wilkinson J, Brown J, Farquhar C. Interventions for heavy menstrual bleeding; overview of Cochrane reviews and network meta-analysis. *Cochrane Database of Systematic Reviews* 2022, Issue 5. Art. No.: CD013180. DOI: 10.1002/14651858.CD013180.pub2.

ABSTRACT

Background

Heavy menstrual bleeding (HMB) is excessive menstrual blood loss that interferes with women's quality of life, regardless of the absolute amount of bleeding. It is a very common condition in women of reproductive age, affecting 2 to 5 of every 10 women. Diverse treatments, either medical (hormonal or non-hormonal) or surgical, are currently available for HMB, with different effectiveness, acceptability, costs and side effects. The best treatment will depend on the woman's age, her intention to become pregnant, the presence of other symptoms, and her personal views and preferences.

Objectives

To identify, systematically assess and summarise all evidence from studies included in Cochrane Reviews on treatment for heavy menstrual bleeding (HMB), using reviews with comparable participants and outcomes; and to present a ranking of the first- and second-line treatments for HMB.

Methods

We searched for published Cochrane Reviews of HMB interventions in the Cochrane Database of Systematic Reviews. The primary outcomes were menstrual bleeding and satisfaction. Secondary outcomes included quality of life, adverse events and the requirement of further treatment. Two review authors independently selected the systematic reviews, extracted data and assessed quality, resolving disagreements by discussion. We assessed review quality using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) 2 tool and evaluated the certainty of the evidence for each outcome using GRADE methods. We grouped the interventions into first- and second-line treatments, considering participant characteristics (desire for future pregnancy, failure of previous treatment, candidacy for surgery). First-line treatments included medical interventions, and second-line treatments included both the levonorgestrel-releasing intrauterine system (LNG-IUS) and surgical treatments; thus the LNG-IUS is included in both groups. We developed different networks for first- and second-line treatments. We performed network meta-analyses of all outcomes, except for quality of life, where we performed pairwise meta-analyses. We reported the mean rank, the network estimates for mean difference (MD) or odds ratio (OR), with 95% confidence intervals (CIs), and the certainty of evidence (moderate, low or very low certainty).

We also analysed different endometrial ablation and resection techniques separately from the main network: transcervical endometrial resection (TCRE) with or without rollerball, other resectoscopic endometrial ablation (REA), microwave non-resectoscopic endometrial ablation (NREA), hydrothermal ablation NREA, bipolar NREA, balloon NREA and other NREA.

Main results

We included nine systematic reviews published in the Cochrane Library up to July 2021. We updated the reviews that were over two years old. In July 2020, we started the overview with no new reviews about the topic. The included medical interventions were: non-steroidal anti-inflammatory drugs (NSAIDs), antifibrinolytics (tranexamic acid), combined oral contraceptives (COC), combined vaginal ring (CVR), long-cycle and luteal oral progestogens, LNG-IUS, ethamsylate and danazol (included to provide indirect evidence), which were compared to placebo. Surgical interventions were: open (abdominal), minimally invasive (vaginal or laparoscopic) and unspecified (or surgeon's choice of route of) hysterectomy, REA, NREA, unspecified endometrial ablation (EA) and LNG-IUS. We grouped the interventions as follows.

First-line treatments

Evidence from 26 studies with 1770 participants suggests that LNG-IUS results in a large reduction of menstrual blood loss (MBL; mean rank 2.4, MD −105.71 mL/cycle, 95% CI −201.10 to −10.33; low certainty evidence); antifibrinolytics probably reduce MBL (mean rank 3.7, MD −80.32 mL/cycle, 95% CI −127.67 to −32.98; moderate certainty evidence); long-cycle progestogen reduces MBL (mean rank 4.1, MD −76.93 mL/cycle, 95% CI −153.82 to −0.05; low certainty evidence), and NSAIDs slightly reduce MBL (mean rank 6.4, MD −40.67 mL/cycle, −84.61 to 3.27; low certainty evidence; reference comparator mean rank 8.9). We are uncertain of the true effect of the remaining interventions and the sensitivity analysis for reduction of MBL, as the evidence was rated as very low certainty.

We are uncertain of the true effect of any intervention (very low certainty evidence) on the perception of improvement and satisfaction.

Second-line treatments

Bleeding reduction is related to the type of hysterectomy (total or supracervical/subtotal), not the route, so we combined all routes of hysterectomy for bleeding outcomes. We assessed the reduction of MBL without imputed data (11 trials, 1790 participants) and with imputed data (15 trials, 2241 participants). Evidence without imputed data suggests that hysterectomy (mean rank 1.2, OR 25.71, 95% CI 1.50 to 439.96; low certainty evidence) and REA (mean rank 2.8, OR 2.70, 95% CI 1.29 to 5.66; low certainty evidence) result in a large reduction of MBL, and NREA probably results in a large reduction of MBL (mean rank 2.0, OR 3.32, 95% CI 1.53 to 7.23; moderate certainty evidence). Evidence with imputed data suggests hysterectomy results in a large reduction of MBL (mean rank 1.0, OR 14.31, 95% CI 2.99 to 68.56; low certainty evidence), and NREA probably results in a large reduction of MBL (mean rank 2.2, OR 2.87, 95% CI 1.29 to 6.05; moderate certainty evidence). We are uncertain of the true effect for REA (very low certainty evidence). We are uncertain of the effect on amenorrhoea (very low certainty evidence).

Evidence from 27 trials with 4284 participants suggests that minimally invasive hysterectomy results in a large increase in satisfaction (mean rank 1.3, OR 7.96, 95% CI 3.33 to 19.03; low certainty evidence), and NREA also increases satisfaction (mean rank 3.6, OR 1.59, 95% CI 1.09 to 2.33; low certainty evidence), but we are uncertain of the true effect of the remaining interventions (very low certainty evidence).

Authors' conclusions

Evidence suggests LNG-IUS is the best first-line treatment for reducing menstrual blood loss (MBL); antifibrinolytics are probably the second best, and long-cycle progestogens are likely the third best. We cannot make conclusions about the effect of first-line treatments on perception of improvement and satisfaction, as evidence was rated as very low certainty. For second-line treatments, evidence suggests hysterectomy is the best treatment for reducing bleeding, followed by REA and NREA. We are uncertain of the effect on amenorrhoea, as evidence was rated as very low certainty. Minimally invasive hysterectomy may result in a large increase in satisfaction, and NREA also increases satisfaction, but we are uncertain of the true effect of the remaining second-line interventions, as evidence was rated as very low certainty.

PLAIN LANGUAGE SUMMARY

Which is the best treatment for heavy menstrual bleeding?

Key results

Evidence suggests that the levonorgestrel-releasing intrauterine system (LNG-IUS) is the best first-line option for reducing menstrual bleeding, while antifibrinolytics are probably the second best, and long-cycle progestogens are the third best. Because of some limitations in the evidence, we are not sure what the true effect of these first-line treatments is for the perception of improvement and satisfaction.

For second-line treatments, evidence suggests any type of hysterectomy is the best treatment for reducing bleeding, even though this is a major surgery, and resectoscopic endometrial ablation (REA) and non-resectoscopic endometrial ablation (NREA) are second and third best. We are uncertain of the true effect of the second-line treatments on amenorrhoea (absence of menstrual blood loss). Evidence suggests that minimally invasive hysterectomy results in a large increase in satisfaction, and NREA increases satisfaction, but we are uncertain of the true effect of the remaining interventions.

What is heavy menstrual bleeding?

Heavy menstrual bleeding is defined as excessive menstrual blood loss that interferes with the quality of life of people who menstruate. It is very common and can affect 20% to 50% of people who menstruate during their reproductive years. There are different treatments available, each with their own pros and cons. The best treatment depends on the person's age, whether they have or want to have children, their personal preferences, and their medical history, among other things.

What did we want to find out?

We wanted to get an overview of all the published evidence on different treatments for heavy menstrual bleeding. We were most interested in finding out if the treatments were effective for reducing menstrual bleeding and for improving women's satisfaction. We also wanted to know how the treatment affected quality of life, what side effects it caused, and whether women required further treatment.

What did we do?

This study is an overview of reviews, which means we looked for published studies that synthesised the results of other studies on different treatments for heavy menstrual bleeding. Then we tried to give a broad overview of all that evidence. We analysed the certainty of the evidence based on factors like study size and methodological rigour. We categorised the treatments based on patient characteristics, including the desire (intention) for future pregnancy, failure of previous treatment or having been referred for surgery. First-line treatment included medical interventions and second-line treatment included the LNG-IUS plus surgical interventions; thus, the LNG-IUS was included in both first- and second-line treatments. We used network meta-analysis, a statistical method that compares all the interventions at the same time, to find out which treatments produced the best results for patients.

What did we find?

We found nine reviews with 104 studies, involving a total of 11,881 participants. Altogether, the data we analysed came from 85 trials and 9950 participants. The medical interventions included were: non-steroidal anti-inflammatory drugs (NSAIDs), antifibrinolytics (tranexamic acid), combined oral contraceptives (COC), combined vaginal ring (CVR), long-cycle and luteal oral progestogens, the LNG-IUS, ethamsylate and danazol (included only to provide indirect evidence). These were compared to placebo (sham treatment). The surgical interventions included were: open (abdominal), minimally invasive (vaginal or laparoscopic) and unspecified (or surgeon's choice of) route of hysterectomy, REA, NREA and unspecified endometrial ablation (EA).

What are the limitations of the evidence?

Our confidence in some evidence is moderate, but for most of it, our confidence is low to very low. The main reasons were because the studies were often not blinded, which means the participants knew which treatment they were receiving, and that could have changed their perception; the direct and indirect evidence was not similar enough to compare in the network; and the range of the results was too wide.

How up to date is this evidence?

The last search for reviews was in July 2021.

BACKGROUND

Description of the condition

Heavy menstrual bleeding (HMB) is excessive menstrual blood loss that interferes with the physical, emotional, social and material quality of life of people who menstruate, and it can occur alone or in combination with other symptoms (Munro 2012; NICE 2018a), such as dysmenorrhoea, fatigue or headache. HMB can lead to other serious health issues, such as iron deficiency anaemia, which occurs in one in four people with HMB (Morrison 2008).

Abnormal uterine bleeding is often used interchangeably with HMB. However, abnormal uterine bleeding is much broader and includes many gynaecological diseases. The International Federation of Gynecology and Obstetrics (FIGO) classifies the gynaecological diseases related to abnormal uterine bleeding as having structural causes (polyp, adenomyosis, leiomyoma, malignancy, and hyperplasia); being unrelated to structural causes (coagulopathy, ovulatory dysfunction, endometrial dysfunction, and iatrogenic); or as not yet classified (Munro 2012). This review will be restricted to HMB.

HMB is objectively defined as menstrual blood loss of 80 mL or more per menstrual period (Cole 1971; Hallberg 1966), which is not related to pregnancy or any systemic condition (for example, bleeding or thyroid disorders) or gynaecological disease. HMB is also known as menorrhagia.

Historically, the gold standard for objectively assessing menstrual bleeding is the haematin alkaline method: this requires the woman to provide all the pads and tampons she uses, and then in the laboratory, a sodium hydroxide solution allows calculation of haemoglobin, and thus of the amount of menstrual bleeding (Shaw 1972). However, in a clinical setting, the objective measurement of menstrual blood loss is impractical (Edlund 2011). Currently, with the clinical diagnosis centred on the women's perception of HMB, the measured amount of blood loss has a secondary role; rather, evaluating the clinical success of treatment should be focused on the woman's perception of improvement.

The prevalence of HMB based on objective measurement ranges from 9% to 14%, but in studies that subjectively assess HMB, it is as high as 20% to 52% (Fraser 2009; NICE 2007). In England and Wales, every year around 30,000 women undergo surgical treatment for HMB (RCOG 2012). HMB is estimated to account for around 30% of total gynaecological visits in the USA and represents an important encumbrance for more than 10 million women (Liu 2007; Miller 2015). Treatment costs ascend to approximately USD 1.3 billion, and lost productivity to around USD 12 billion to USD 36 billion per year (Liu 2007; Miller 2015). In Japan, 19% of women 15 to 49 years of age reported HMB (Tanaka 2013). In low- and middle-income countries, the incidence of HMB appears to be similar to that of high-income countries, although data are limited (Haththotuwa 2011). Data from a systematic review in 2004 assessing the epidemiology of menstrual disorders in low- and middle-income countries reported a prevalence of HMB of 15%, ranging from 5% in rural Gambia to 20% in China (Harlow 2004).

The prevalence of HMB varies by age. In a population-based prevalence study with nearly 1000 healthy adolescent girls, approximately 40% had experienced HMB (Friberg 2006). The annual rate of presentation to health services with HMB in the UK is around 2% before the age of 40 and increases to 5% between 45 and 49 years of age (NICE 2007). A Swedish study conducted to assess quality of life in women with HMB reported that prevalence in women aged 40 to 45 years was 32% (Karlsson 2014).

Adequate assessment, followed by appropriate treatment, considerably improves the quality of life of women with HMB (Hurskainen 2007).

Description of the interventions

Diverse medical and surgical treatments are available for treating HMB, with different effectiveness, tolerability, acceptability and cost for the patient. The woman's age, intention to become pregnant, associated symptoms, preferences and values are important for selecting the treatment.

First-line treatments for HMB include all medical interventions (non-hormonal and hormonal). Second-line treatments include the levonorgestrel-releasing intrauterine system (LNG-IUS) and all surgical interventions; they may be appropriate when previous medical treatment has failed, when women have completed their family or when they are surgical candidates. LNG-IUS is considered both a first- and second-line treatment.

Medical interventions

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs, such as ibuprofen and mefenamic acid, are a non-hormonal oral medical intervention. NSAIDs have potent anti-inflammatory, analgesic and antipyretic activity and are among the most widely used drugs worldwide (Bacchi 2012). NSAIDs should be avoided in women with severe asthma, gastrointestinal ulceration or kidney disease.

Antifibrinolytic agents

Tranexamic acid is the most commonly used antifibrinolytic agent. Antifibrinolytics should be avoided in women with thromboembolic disease or a history of convulsions (Lecker I 2016).

Combined hormonal contraceptives

Combined hormonal contraceptive methods contain oestrogen and progestin. There are different regimens and delivery routes available, including oral, vaginal, transdermal and intramuscular. Not all delivery routes have been assessed for the management of HMB. Combined hormonal contraceptives have been linked to a higher risk of thrombotic side effects, although the oestrogen dose has been gradually reduced from 150 µg in the original preparations to 30 µg or less at the time of writing, which has reduced the risk considerably (Speroff 2010). Combined hormonal contraceptives are still associated with a small increased risk of venous thromboembolism (De Bastos 2014). This overview included two different types of combined hormonal contraceptives: combined oral contraceptive (COC) and combined vaginal ring (CVR).

Cyclical oral progestogens

During the 1990s, oral progestogens were the most commonly prescribed drug for HMB (Coulter 1995). Oral progestogens can be taken during the luteal phase (day 14 to 24 of the menstrual cycle) or as an extended regimen for 20 to 25 days per cycle. Cyclical progestogens are not contraceptives. The prolonged use of high-

dose progestogens is associated with side effects, such as weight gain, nausea, headaches and decreased libido.

Progestogen-releasing intrauterine systems (Pg-IUS or LNG-IUS)

The progesterone-releasing intrauterine systems are small T-shaped systems, inserted into the uterine cavity through the cervix, releasing small amounts of a progestogen (levonorgestrel) locally. The LNG-IUS is available in different formats with varying doses of levonorgestrel released over varying periods.

Danazol (†)

Danazol is an oral drug that interferes with the pituitary gland, preventing the secretion of follicle-stimulating hormone and luteinising hormone. Danazol is contraindicated in pregnancy and should be used along with safe contraception in sexually active women (Brunskill 1992). Danazol is currently used for a myriad of haematological conditions (Audia 2016), and it used to be commonly prescribed for HMB during the 1990s. However, although its adverse events are infrequent, other safer and fairly similarly effective alternatives are available. Reported adverse events are usually androgenic and anti-oestrogenic, and haematologically can be either anticoagulant or procoagulant (Alvarado 2001). In a cohort of 530 patients, 29% reported at least one adverse event: 6% androgenic, 6% hypo-oestrogenic, 12% some combination and 5% other non-androgenic and non-hypo-oestrogenic (Jick 1995). Danazol has also been linked to liver damage (Alvaro 1996).

(†) Despite being effective in reducing menstrual bleeding, its adverse events advise against its use for HMB. We included danazol in this overview to provide indirect comparisons in the network meta-analysis.

Ethamsylate

Ethamsylate is a synthetic haemostatic drug used for capillary bleeding (Garay 2006). It was widely used for HMB in the 1970s and 1980s (Harrison 1976). With less promising results, its use for HMB over the past 20 years has been negligible ((D) Bonnar 1996; Bongers 2004). We included ethamsylate in this overview to provide indirect comparisons in the network meta-analysis.

Surgical interventions

Endometrial resection and ablation

Endometrial resection and endometrial ablation (EA) are different techniques aiming to remove or destroy the endometrium (inner layer of the uterus). They are usually categorised by generation: first-generation techniques require direct visualisation of the uterine cavity, while second- or third-generation procedures do not. Although these categories are widely used in the literature, there is evidence that endometrial ablation started in the late 19th century with non-resectoscopic techniques (Famuyide 2018). In 1894, Sneguireff applied steam to arrest profuse bleeding during the removal of a parasitic liver cyst and then started using it to control surgical bleeding on the lungs, kidneys, long bones and, eventually, uterine bleeding in women (Famuyide 2018). In the late 1890s, the equipment was improved, adding some safety features and defining indications and contraindications (Blacker 1902). Simultaneously, Pincus defined two types of procedures: atmocausis, which used steam directly on the endometrium, and zestocausis, which used metal to provide the heat (Famuyide 2018; Pincus 1899a; Pincus 1899b). Honouring the first attempts of endometrial ablation, we will use the categories based on the procedures' characteristics (Famuyide 2018; Munro 2018).

Resectoscopic endometrial ablation (REA) involves different forms of energy delivered through an operative hysteroscope to remove or destroy the endometrium, such as electrocoagulation or desiccation, transcervical endometrial resection (TCRE), or vaporisation (Munro 2018).

Non-resectoscopic endometrial ablation (NREA) is a group of devices designed to destroy the endometrium without a resectoscope (not requiring fluid distention of the uterine cavity). Although it is a non-hysteroscopic technique, pre- and postprocedure diagnostic hysteroscopy or intraprocedural ultrasound guidance may be useful for safety and intracavitary device placement (Laberge 2015).

Hysterectomy

Hysterectomy is a major surgical procedure, consisting of removing the uterus, with or without the adnexa. Some examples of hysterectomy complications are infection, thromboembolic complications, genitourinary and gastrointestinal tract injuries, bleeding and vaginal cuff dehiscence (Clarke-Pearson 2013). The complications vary depending on the route and the surgical technique.

How the intervention might work

Medical interventions

Non-steroidal anti-inflammatory drugs (NSAIDs)

The endometrium of women with HMB has high prostaglandin levels compared to women with normal menstrual bleeding. NSAIDs (such as mefenamic acid and ibuprofen, among others) reduce prostaglandin levels by inhibiting the enzyme cyclooxygenase (Rees 1987; Smith 1981). NSAIDs taken regularly during menses can alleviate HMB.

Antifibrinolytic agents

Increased levels of plasminogen activators (group of enzymes that cause fibrinolysis) have been found in the endometrium of women with HMB compared to women with normal menstrual bleeding (Gleeson 1994). Tranexamic acid is a true plasminogen activator inhibitor, making it an alternative drug for reducing menstrual bleeding.

Combined hormonal contraceptives

Combined hormonal contraceptives contain different combinations of oestrogen and progestin. Oestrogen provides negative feedback on follicle-stimulating hormone secretion and prevents the development of a dominant follicle (Bradley 2016), providing endometrial stability and growth, improving the progestational impact. At the same time, progestin impedes the rise of luteinising hormone and consequently prevents ovulation and creates an atrophic endometrial lining. This combination reduces overall menstrual blood loss (Fritz 2012). Different routes of delivery have been assessed to manage HMB (Uhm 2014), such as the CVR and oral contraception ((D) Dahiya 2016; Micks 2013).

Cyclical oral progestogens

The role of progestogens in treating HMB might work "by stabilizing endometrial fragility; inhibiting the growth of the endometrium by triggering apoptosis; inhibiting angiogenesis; and stimulating the conversion of estradiol to the less active oestrone" (Fritz 2012). Progestogens can be used in different regimens, either during the entire cycle, during the luteal phase only, or for a longer period of 20 to 25 days. When used as a long-course treatment, oral progestogens prevent ovulation and ovarian steroidogenesis. As a consequence, they discontinue the production of oestrogen receptors and the oestrogen-dependent stimulation of the endometrium, leading to an atrophic endometrium (Bradley 2016).

Progestogen-releasing intrauterine systems

With this device, hormones are released locally into the uterine cavity, resulting in high progestogen levels in the endometrial tissue but low systemic circulation levels. As a consequence of the local action of the progesterone, endometrial growth is suppressed (Herman 2013), and in turn, menstrual bleeding decreases.

Danazol

Danazol is a synthetic steroid ethisterone. It prevents pituitary secretion of follicle-stimulating hormone and luteinising hormone. Danazol has a weak androgenic influence, producing atrophy of endometrial tissue, which reduces menstrual loss and may lead to amenorrhoea in some women ((N) Chimbira 1980).

Surgical interventions

Endometrial resection and ablation

Endometrial resection and endometrial ablation destroy the endometrium (lining of the cavity of the uterus). They are safe, effective, minimally invasive procedures, performed through the cervix, with different methods for removing (resection) or destroying (ablation) the endometrium (Kumar 2016).

Hysterectomy

Although surgically removing the uterus is invasive, it represents the most definitive treatment option for HMB. It is important to assess the relative risk and the plans for future childbearing before making the decision. There are four different surgical approaches: abdominal hysterectomy, vaginal hysterectomy, laparoscopic hysterectomy and robot-assisted laparoscopic hysterectomy (Van der Heijden 2017).

Why it is important to do this overview

HMB has a high prevalence amongst otherwise healthy women of reproductive age. Different interventions are currently available, including pharmacological treatments (hormonal and non-hormonal) and surgical procedures. This overview aims to assess and rank the safety and efficacy of the treatments with regard to blood loss reduction, satisfaction with treatment, quality of life, adverse effects and treatment failure, and to summarise the data in an accessible way for patients and their families, physicians, healthcare providers and policymakers. Network meta-analysis compares more than two interventions at the same time. This allows the comparison of interventions that have not been compared directly in the studies, as long as they form a connected network, providing a complete summary of evidence. There is an overview of interventions for HMB available during pandemics (Bofill Rodriguez 2020a), which was developed in 2020 and inspired by the challenges of the pandemic to the health system; it includes only medical interventions that required minimal (or no) face-to-face contact; thus, it did not include LNG-IUS or any surgical procedure. It also only reported pairwise meta-analysis.

OBJECTIVES

To identify, systematically assess and summarise all evidence from studies included in Cochrane Reviews on treatment for heavy menstrual bleeding (HMB), using reviews with comparable participants and outcomes; and to present a ranking of the first- and second-line treatments for HMB.

METHODS

Criteria for considering reviews for inclusion

We included Cochrane Reviews of interventions for heavy menstrual bleeding (HMB) in otherwise healthy women, which are published in the Cochrane Library; we did not include non-Cochrane reviews in the overview. Not all studies included in the Cochrane Reviews contributed data to the overview, only studies reporting on the overview outcomes. The references to studies contributing with data to the overview are in the 'Additional references' section and are designated by a (D) for data prefacing the name of the study.

We have formulated our overview in the PICO (participants, interventions, control, outcome) format.

Type of participants

Women in reproductive years with HMB, assessed objectively or semi-objectively, using the haematin alkaline method, pictorial blood assessment chart (PBAC), or patient perception of HMB.

We conducted a subgroup analysis based on whether the participants were surgical candidates or not. We considered the 'the desire (or intention) of future pregnancy', 'women completed their families', 'with indication of hysterectomy' or 'medical treatment failure' as inclusion or exclusion criteria to determine if the participants were surgical candidates. According to that, we performed the network meta-analysis for first- or second-line treatment. The progestogen-releasing intrauterine system (LNG-IUS) was part of both groups.

Type of interventions

We included medical and surgical treatments for HMB that were included in Cochrane Reviews.

Medical interventions

- Nonsteroidal anti-inflammatory drugs
- Antifibrinolytic agents
- Combined hormonal contraceptives divided according to the delivery route in combined oral contraceptives and combined vaginal ring
- Cyclical oral progestogens, divided by the length of the cycle in luteal-phase or long-cycle oral progestogens (three to four weeks per cycle)
- Progestogen releasing intrauterine system

- Danazol and ethamsylate (included only to provide indirect evidence)

Progestin-only contraceptives, such as injections and implants, usually reduce menstrual blood loss in the general population and can cause amenorrhoea (Di Carlo, 2015; Jacobsten 2014). They are commonly used off-label for HMB; we performed a search on the topic. See Appendix 1 for details.

Surgical interventions

- Resectocopic endometrial ablation (REA), categorised as transcervical endometrial resection, with or without rollerball, and other REA
- Non-resectoscopic endometrial ablation (NREA), categorised as microwave NREA, hydrothermal ablation NREA, bipolar NREA, balloon NREA and other NREA
- Hysterectomy, categorised by the route: minimally invasive (vaginal or laparoscopic), open (abdominal) and unspecified (or route at surgeon's discretion)

Control

We compared interventions with placebo or no intervention and with other interventions.

Types of outcome measures

Primary outcomes

- Menstrual bleeding reduction
  - Objectively assessed by the haematin alkaline method, mean blood loss during treatment, mean reduction of blood loss from baseline during treatment or mean blood loss at different periods
  - Semi-objectively assessed using the PBAC, mean difference of PBAC at different periods or the proportion of women with reduction in bleeding as measured by PBAC under different cutoffs
  - Subjectively assessed patient perception of HMB: participants' perceived blood loss (better, same, worse)
  - Prevalence of amenorrhoea or hypomenorrhoea after treatment
- Satisfaction with treatment at one year follow-up, reported as a dichotomous outcome as the proportion of women satisfied with treatment. Some trials reported this using a four-level scale questionnaire, either very satisfied, satisfied, somewhat dissatisfied, dissatisfied, or liking treatment very well, well, moderately, poorly; in both cases, we considered the two first categories satisfactory.

Secondary outcomes

- Quality of life improvement: women's perceived change in quality of life, where it was recorded in a reproducible and validated format
- Adverse effects of any severity recorded within the included Cochrane Reviews
- Requirement of further surgery or additional medical treatment at one year follow-up.

Search methods for identification of reviews

We searched the Cochrane Database of Systematic Reviews (CDSR) in the Cochrane Library for any reviews with heavy menstrual bleeding (HMB) or menorrhagia in the title, abstract or keyword fields. The last search was in July 2021.

Data collection and analysis

Selection of reviews

Two overview authors (MBR and JB) independently assessed all potentially eligible reviews identified by the search strategy. We resolved any disagreements by discussion. During the first review search, one of the authors was involved in one HMB review (JB, combined hormonal contraceptives for HMB), and the other (MB) was not involved in any reviews.

We created 'Characteristics of reviews' tables, including the following information: review title; author team; number of included trials and participants; participant characteristics (inclusion and exclusion criteria); interventions and comparisons; primary and secondary outcomes and date of the last search.

Data extraction and management

Two review authors (MB and VJ) independently extracted data from each included review, resolving any disagreements by discussion or adjudication by a third overview author. In order to obtain data in a valid format for the network meta-analysis (NMA), we extracted data from individual studies contributing to each of the outcomes. We summarised key information from each study contributing to the NMA on the data extraction form, including participant's details, the interventions, comparisons and outcomes (see Table 1 and Table 2 for the characteristics of studies contributing to the NMA). Outcomes were focused on bleeding reduction, satisfaction, improvement of quality of life and adverse effects.

We extracted the following characteristics from each included Cochrane Review.

1. Review title and authors.
2. Date that the review was last assessed as up-to-date or declared a stable review.
3. Number of trials.
4. Number of participants.
5. Participant characteristics.
6. Inclusion criteria.
7. Exclusion criteria.
8. Outcomes.
9. Where available, the GRADE assessment and any relevant comments made in the review's 'Summary of findings' table regarding trial quality and risk of bias (only for pairwise meta-analysis).

For the trials contributing to the NMA, we extracted the same information except for the GRADE assessment, as it is not available for individual studies.

We solved any disagreements by discussion between the author team. We contacted review and trial authors where necessary to clarify data included in the reviews.

Where multiple Cochrane Reviews used the same data, we used it only once to avoid duplication of evidence and consequent double-counting of trial data. We reconciled data across the various reviews to ensure that all the information on each arm of the study was included appropriately. If there was any discrepancy between reviews, two review authors reviewed the original publication. As we anticipated in the protocol, we had various trials of treatment for HMB in more than one review.

As the Review Manager (RevMan) format for overviews allows the inclusion of reviews only, we added the individual studies providing data for the NMAs in the additional references adding a (D), as in data, for easy access and to differentiate them from additional references, and with (N) for the studies that were included but did not contribute data to the NMA.

Assessment of methodological quality of included reviews

Methodological quality of included Cochrane Reviews

Two overview authors assessed the included reviews with the AMSTAR 2 quality measurement tool (Shea 2017). SL assessed all of the reviews, MW assessed five reviews, MB assessed three reviews and VJ assessed one review (to avoid review authors assessing the quality of their own reviews). The overview authors solved any discrepancies by discussion; when necessary, a third overview author was included to adjucate (CF).

The original AMSTAR tool included 11 items (Shea 2007); the new AMSTAR 2 tool includes 16 items in total, and the response categories are simpler with a more comprehensive user guide, including reasons for the final assessment. The final assessments are rated 'yes', 'partial yes' or 'no'. The overall rating is based on weaknesses in critical domains (Shea 2017). See Appendix 2 for AMSTAR 2 details.

Quality of trial evidence included in Cochrane Reviews

We did not reassess the risk of bias for trials included in reviews, as they were assessed in the original reviews. Studies in the danazol review (which has not been updated) were also included in fully assessed reviews. There were only a few inconsistencies between reviews in the risk of bias assessment. When inconsistency was present, one overview author (MB) acted as a third party, checking the reasons for the assessment and the original trials and discussing the assessments with another overview author (CF). For example, review authors judged one study as being at uncertain risk of bias for all categories, as they only had access to a short conference publication and were not able to contact the authors, while in another review, review authors had access to an unpublished copy of the study; thus we used the risk of bias assessment of the review with access to the data. In one review, review authors rated three studies as being at high risk, and in another review, the authors rated the risk of bias as unknown for not mentioning either allocation or blinding; we considered the risk to be unknown. In another review, authors rated one trial from the 1990s as being at high risk of selective reporting because it did not have a protocol, but another review rated the risk as low because the study reported all the pre-specified outcomes; we considered it to be at low risk.

Where possible, for pairwise comparisons, we used the Cochrane Review authors' GRADE assessments of relevant outcomes, as presented in the summary of findings tables of included Cochrane Reviews. Where GRADE summaries were not available for our outcomes, two overview authors (MBR and AL) independently assessed the quality using GRADEpro (GRADEpro GDT 2015). The GRADE summary of findings in a Cochrane Review includes an overall judgement of the risks of bias in the specific trials contributing data to the pooled effect estimate for each outcome displayed in the table. In addition to the risk of bias, for each outcome the GRADE assessment takes into consideration the following domains: imprecision of effects (due to wide confidence intervals, sparse data or both); unexplained inconsistency between trials (as measured by the I^2 statistic value/heterogeneity); indirectness (differences in the population, intervention, comparison or outcome of trials); and evidence of publication bias, where the meta-analysis includes sufficient trials. Pooled evidence for randomised controlled trials (RCTs) with serious problems in any of these domains is downgraded one level. If problems are very serious, we may downgrade evidence by two levels. The Guideline Development Tool assesses these downgrading decisions and assigns the pooled estimate for each outcome a rating of either high, moderate, low or very low certainty (GRADE handbook; GRADEpro GDT 2015; Guyatt 2008). There are standard definitions to aid the interpretation of GRADE ratings, as follows.

- High: further research should not alter our confidence in evidence rated as high certainty.
- Moderate: future research will likely impact our confidence in moderate certainty evidence and could change the estimates.
- Low or very low: there is considerable uncertainty surrounding the effect estimates considered to be of low or very low certainty, and further research will impact our confidence in these effect estimates and change the estimates (Guyatt 2008; Guyatt 2011a).

We intended to exclude evidence of low or very low certainty, as the GRADE rating of evidence is an important finding of the overview. Unfortunately, as most trials were at high risk of performance bias, most of the evidence was low certainty, so we included it.

A GRADE assessment may be further translated into a summary statement that incorporates the clinical importance of the effect, for clarity, using the following guide.

We have interpreted the evidence following the 'GRADE guidelines 26: Informative statements to communicate the findings of systematic reviews of interventions' by Santesso 2020.

For outcomes subject to NMA, we present a summary of findings table, adapted from Yepes-Nunez 2019. For NMA, one summary of findings table is produced for each outcome and contains effect estimates, credible intervals or confidence intervals, certainty of evidence (for each included intervention compared to one comparator) and a ranking. The NMA summary of findings table from Yepes-Nunez 2019 reports the number of trials and patients providing direct evidence between the intervention and the common comparator and uses credible intervals. We adapted the table, including the number of trials and participants providing direct evidence for each intervention, and we reported confidence intervals.

The certainty of the evidence for each intervention takes into account both the certainty of the evidence provided by direct and indirect comparisons, inconsistency or incoherence (consistency

between direct and indirect evidence), and imprecision (of the network estimate).

To rate the certainty of evidence of the NMA and interpret it, we considered the direct, indirect and network estimate for each comparison and outcome (Brignardello-Petersen2017; Brignardello-Petersen 2019; Puhan 2014). The rating of the direct estimate considered the risk of bias, inconsistency-heterogeneity, indirectness and publication bias of the direct evidence. If the direct evidence was of high certainty and direct evidence contributed as much as the indirect, we intended to rate the network estimate directly (no comparison was rated of high certainty evidence). If it was moderate, low or very low certainty, we rated the indirect estimate. We rated the indirect evidence considering the most dominant first-order loop (if available, and if more than one was available we intended to choose the one with a larger number of participants and trials), looking at its direct estimates. Indirect evidence was rated lower than the direct evidence providing evidence on the loop. A loop is a section of the network diagram, with three or more interventions interconnected with direct evidence, and each direct source of evidence can be complemented by an indirect source of evidence for the same comparison. The certainty was considered to be the same as whichever piece of direct evidence on the loop had the lowest certainty. The indirect evidence was also assessed for transitivity. The transitivity assumption requires that the distribution of effect modifiers be similar for all sources of direct evidence (Salanti 2014); this was evaluated conceptually. Finally, we rated the network estimate, choosing the estimate that contributed the most to the comparison (either directly or indirectly, or the highest if both contributed similarly and there was no incoherence) and examined for incoherence (inconsistency test) and imprecision (intervals and direction of effect).

We did not interpret the findings from the NMA as proposed by Brignardello-Petersen 2020, as we did not have a threshold of clinical significance for the outcomes.

Data synthesis

Types of outcomes

We included Cochrane Reviews that reported one or both of the primary outcomes: menstrual blood loss reduction or treatment satisfaction. We included clinically important secondary outcome measures, such as quality of life, side effects and requirement of further treatment. We planned to impute data where missing for primary outcomes and conduct a sensitivity analysis, testing such results with and without the imputed data.

Data synthesis and presentation

We organised the review evidence for each subgroup (first and second-line treatments).

NMA is a method that allows synthesis of information from a network of trials assessing the same question, but comparing different interventions. It allows inferences on interventions that have not been compared directly in any studies and can increase the precision for comparisons with limited data (Caldwell 2014; Salanti 2014). NMA enables comparisons using direct and indirect evidence simultaneously and can rank all interventions coherently. Direct evidence is obtained from trials that directly compare two or more interventions, and indirect evidence is also combined when two interventions have been compared to a common comparator. With NMA it is possible to compare multiple interventions at the same time, even if some of them have not been compared to each other. However, the network needs to be connected. The interventions in each NMA are represented by a diagram, where nodes represent the interventions, and the size of the nodes is proportional to the number of participants randomised to that intervention. Nodes are connected by lines; the width of the lines is proportional to the number of trials available for that comparison. An NMA requires included studies to be sufficiently similar so that the distribution of the effect modifiers is similar for all sources of direct evidence (Higgins 2021; Salanti 2014). This is referred to as consistency (also coherence or transitivity) (Dias 2019).

We conducted network meta-analysis using the Stata 16 network package (White 2015), as RevMan does not support NMA; the NMA model estimation was based on multivariable meta-analysis. We conducted the NMA using individual studies from the included reviews (checking and deleting duplicates), for the following outcomes.

- First-line treatments.
  - Menstrual blood loss reduction: mean blood loss (combining mean blood loss at the end of treatment and change from baseline); mean blood loss at the end of treatment (sensitivity analysis); and perception of bleeding improvement.
  - Satisfaction.
  - Adverse events: side effects and serious adverse events.
- Second-line treatments.
  - Menstrual blood loss reduction: PBAC reduction; proportion with blood loss of PBAC under 75 mL (normal menstrual blood loss) or acceptable improvement (participant perception).
  - Satisfaction.
  - Requirement of further surgery (endometrial ablation or hysterectomy) up to one year follow-up.

Bleeding reduction, and in consequence the requirement of further surgery for treatment failure, are not related to the route of hysterectomy but rather the type of hysterectomy (total or supracervical/subtotal), so we combined all routes of hysterectomy for bleeding outcomes and requirement of further surgery due to treatment failure.

We conducted a second subgroup analysis for endometrial resection and ablation procedures.

We divided the EA subgroup by type of procedure into resectoscopic and non-resectoscopic ablation, and each group into different types using the most common ones, leaving the remaining as a group.

REA was divided in TCRE with or without rollerball, and other REA.

NREA was divided by procedure into microwave NREA, hydrothermal ablation NREA, bipolar NREA, balloon NREA and other NREA. Outcomes were:

- bleeding: amenorrhoea at one year follow-up;
- satisfaction;
- adverse event: perforation;

- requirement of further surgery or HMB treatment: any (EA or hysterectomy) and requirement of further hysterectomy.

We assumed a common estimate for the heterogeneity variance across the different comparisons. Fixed-effect and random-effects models were fitted where possible. Random-effects models were fitted only where there were three or more studies in at least one treatment comparison. We inspected the heterogeneity estimate, Tau, and where it was close to zero, we presented results for the fixed-effect model. Where Tau was moderate to large, we presented results for the random-effects model. We compared Tau to the size of the estimated relative effects and considered it in relation to the scale of the outcomes. Where Tau was consistently larger than the estimated relative treatment effects when considered on the same scale, we qualitatively described it as large, since this implies that the variability between relative treatment effects can be larger than the effects themselves. Where Tau was similar or smaller than the estimated relative effects, we qualitatively described it as moderate.

For the selected model (fixed-effect or random-effects), we checked consistency for each network using the node-split model and inconsistency models (Dias 2010; Dias 2018; Van Valkenhoef 2016; White 2015). If evidence of inconsistency in loops using the node-split model or overall inconsistency model was detected ($P < 0.05$), we attempted to explain it by checking the data and study inclusion for errors. Where we could not identify an explanation, we expressed caution in interpreting the results. When the inconsistency was extremely high, we did not perform NMA.

We reported the network estimates for mean difference (MD) or odds ratio (OR), with 95% confidence interval (CI), the certainty of evidence (moderate, low or very low), mean rank and the **s**urface **u**nder the **c**umulative **ra**nking curve (SUCRA).

SUCRA is a numeric representation of the overall ranking. It has a single number associated with each treatment, and the values range from 0% to 100%. The larger the SUCRA, the higher the chances a treatment is ranked highest among all the available treatments. On the contrary, the lower the SUCRA, the more likely the intervention is to be ranked near the bottom. We presented a cumulative SUCRA graph for each outcome, which indicates the cumulative probability of being the best treatment, the second-best, etc. until the worst treatment for the specific outcome. Interventions with high probabilities for low-ranking values are likely to be better than interventions starting at low probabilities for low ranks. The ranking goes from best to worst for all outcomes, meaning for positive or good outcomes such as bleeding reduction and satisfaction, a higher rank indicates a higher bleeding reduction or a bigger proportion satisfied with treatment. On the other hand, for negative or bad outcomes, such as adverse events, treatment failure or requirement of further surgery, a higher rank indicates a lower incidence of adverse events, treatment failure and requirement of further surgery.

Where NMA was not conducted (network not connected or inappropriate to pool), we presented the results from pairwise comparisons.

For pairwise comparisons we used risk ratios (RRs) for dichotomous outcomes and MDs for continuous outcomes, with their respective 95% CIs. We used the individual studies used in the reviews. We checked for any duplication, and if more than two studies compared the same treatments, we calculated a random-effects summary in a pairwise meta-analysis.

We used RevMan for pairwise meta-analyses and Stata for NMA (Review Manager 2020; White 2015).

Subgroup analysis

We conducted a subgroup analysis based on whether the participants were surgical candidates or not. We considered that 'the desire (or intention) of future pregnancy', 'women completed their families', 'with indication of hysterectomy' or 'medical treatment failure' as inclusion or exclusion criteria to determine if the participants were surgical candidates. According to that judgement, we performed the NMA for first- or second-line treatment. The progestogen-releasing intrauterine system (LNG-IUS) was part of both groups.

A second subgroup analysis was conducted comparing the different endometrial ablation and resection techniques by type of procedure.

Methodology note

Methodologies for both overviews and NMAs have been developed since the publication of the protocol in 2018. It may be appropriate for the update to consider evolving the overview to a review of interventions, which would facilitate the process, by allowing a single search with all the NMA details, instead of updating each review.

RESULTS

Description of included reviews

In July 2021 we identified 20 Cochrane Reviews on heavy menstrual bleeding.

We included nine reviews in this overview: Beaumont 2007; Bofill Rodriguez 2019a; Bofill Rodriguez 2019b; Bofill Rodriguez 2019c; Bofill Rodriguez 2020; Bofill Rodriguez 2021; Bryant-Smith 2018; Lethaby 2019 and Marjoribanks 2016. The last search was performed after January 2016 in all but Beaumont 2007, a review of danazol that has been stable since 2007. See Figure 1 for details of the selection process.

Figure 1. Review flow diagram

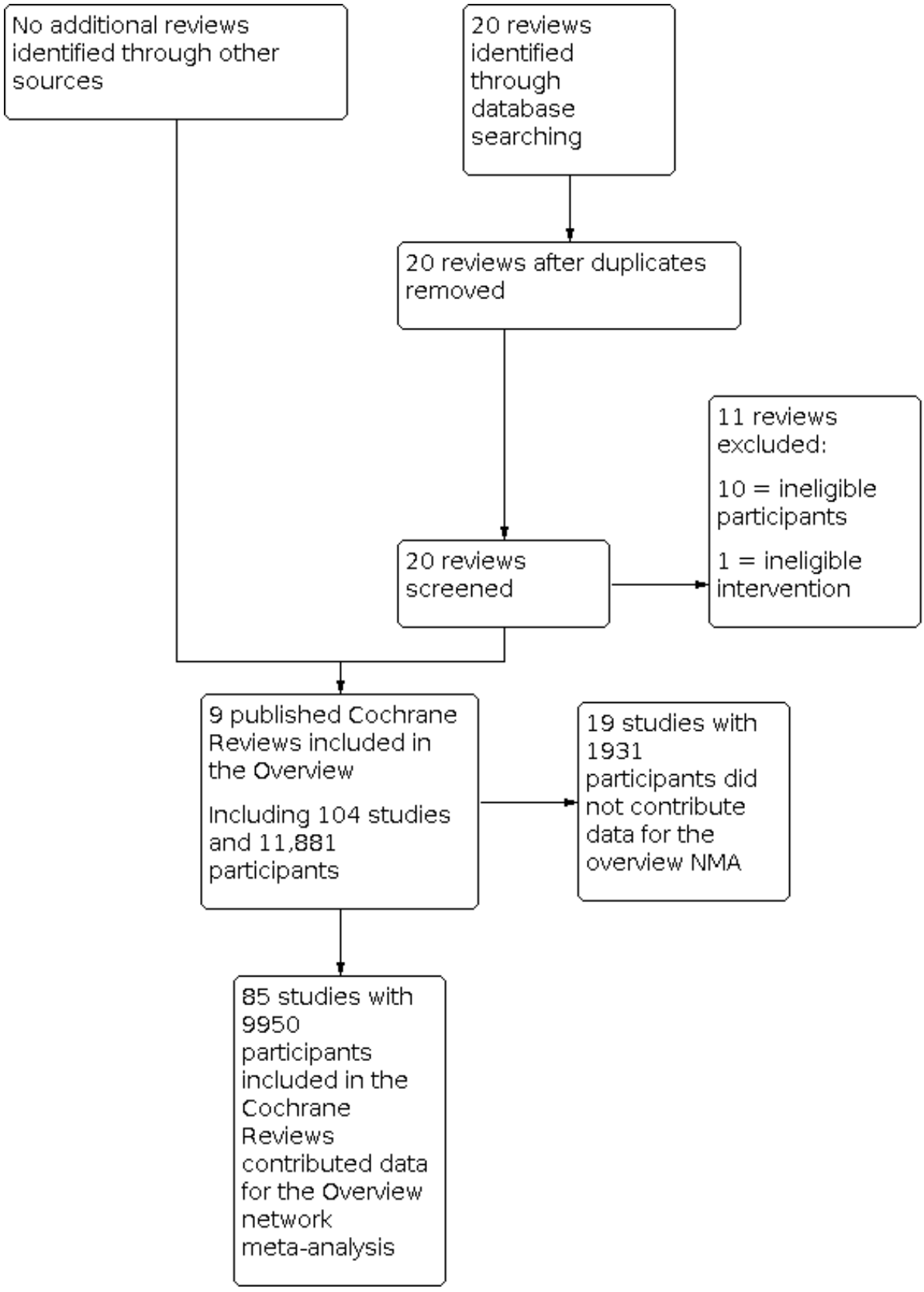


Table 3 presents details of included review characteristics (review title and author, when it was updated, number of studies and participants, type of interventions, inclusion and exclusion criteria and outcomes).

The nine reviews included a total of 138 studies. We identified 26 studies that were part of two reviews and 4 studies that were part of three. After removing the duplicate data, we were left with a final total of 104 unique studies with 11,881 participants.

Nineteen studies with 1931 participants did not contribute data for the following reasons.

- Three because one of the treatment arms was not randomised (it was chosen from several options either by the doctor or the women) ((N) Cooper 1997; (N) Gupta 2013; (N) Kupperman 2004).
- One because the comparison was the same type of intervention (different dosages of danazol) ((N) Chimbira 1980).
- Eight because the data reported did not allow comparisons included in this overview ((N) Andersch 1988; (N) Hall 1987; (N) Khajehei 2013; (N) Lamb 1987; (N) Najam 2010; (N) Onoglu 2007; (N) Reid 2005; (N) Shravage 2011).
- One compared TCRE to rollerball ((N) Boujida 2002).
- Three because the second intervention was not specified in the included interventions of this overview ((N) Fathima 2012; (N) Goshtasebi 2015; (N) Thabet 2010); therefore they do not contribute with indirect evidence.
- Three because the participants had other characteristics; in one, all women had a valve replacement and were receiving anticoagulants ((N) Kilic 2009); in another two, there were different causes of HMB ((N) Cameron 1987; (N) Makarainen 1986).

Altogether, then, 85 studies with 9950 participants contributed data for the overview.

Thirty-five studies with 2702 participants contributed data for the first-line treatments network ((D) Agarwal 2016; (D) Ashraf 2017; (D) Bonduelle 1991; (D) Bonnar 1996; (D) Buyru 1995; (D) Callender 1970; (D) Cameron 1990; (D) Chamberlain; (D) Dahiya 2016; (D) Dockeray 1989; (D) Dunphy 1998; (D) Edlund 1995; (D) Endrikat 2009; (D) Fraser 1981; (D) Fraser 1991; (D) Fraser 2011; (D) Freeman 2011; (D) Goshtasebi 2013; (D) Hashim 2012; (D) Higham 1993; (D) Irvine 1988; (D) Jaisamrarn 2006; (D) Jensen 2011; (D) Kaunitz 2010; (D) Kiseli 2016; (D) Kriplani 2006; (D) Lukes 2010; (D) Muggeridge 1983; (D) Preston 1995; (D) Sayed 2011; (D) Shabaan 2011; (D) Tsang 1987; (D) van Eijkeren 1992; (D) Ylikorkala 1986; (D) Zhang 2008). See Table 1 for characteristics of studies contributing with data to the network meta analysis (NMA).

Fifty studies with 7248 participants contributed data to the second-line treatments network ((D) Abbott 2003; (D) Athanatos 2015; (D) Barrington 2002; (D) Bhattacharya 1997; (D) Bongers 2004; (D) Brun 2006; (D) Clark 2011; (D) Cooper 1999; (D) Cooper 2002; (D) Cooper 2004; (D) Cooper 2019; (D) Corson 2000; (D) Corson 2001; (D) Crosignani 1997; (D) Crosignani 1997a; (D) De Souza 2010; (D) Dickersin 2007; (D) Duleba 2003; (D) Dwyer 1993; (D) Ergun 2012; (D) Gannon 1991; (D) Ghazizadeh 2014; (D) Hawe 2003; (D) Herman 2013; (D) Hurskainen 2004; (D) Istre 1998; (D) Jain 2016; (D) Kittelsen 1998; (D) Laberge 2017; (D) Malak 2006; (D) McClure 1992; (D) Meyer 1998; (D) O'Connor 1997; (D) Ozdegirmenci 2011; (D) Pellicano 2002; (D) Penninx 2010; (D) Penninx 2016; (D) Perino 2004; (D) Pinion 1994; (D) Romer 1998; (D) Sambrook 2009; (D) Sesti 2011; (D) Sesti 2012; (D) Shaw 2007; (D) Soysal 2002; (D) Talis 2006; (D) Tam 2006; (D) van Zon-Rabelink 2003; (D) Vercellini 1999; (D) Zupi 2003). See Table 2 for characteristics of studies contributing with data to the NMA.

See Figure 2 for the risk of bias assessment of studies contributing data to the NMA.

Figure 2. Risk of bias of individual trials contributing with direct evidence for the network meta-analysis.

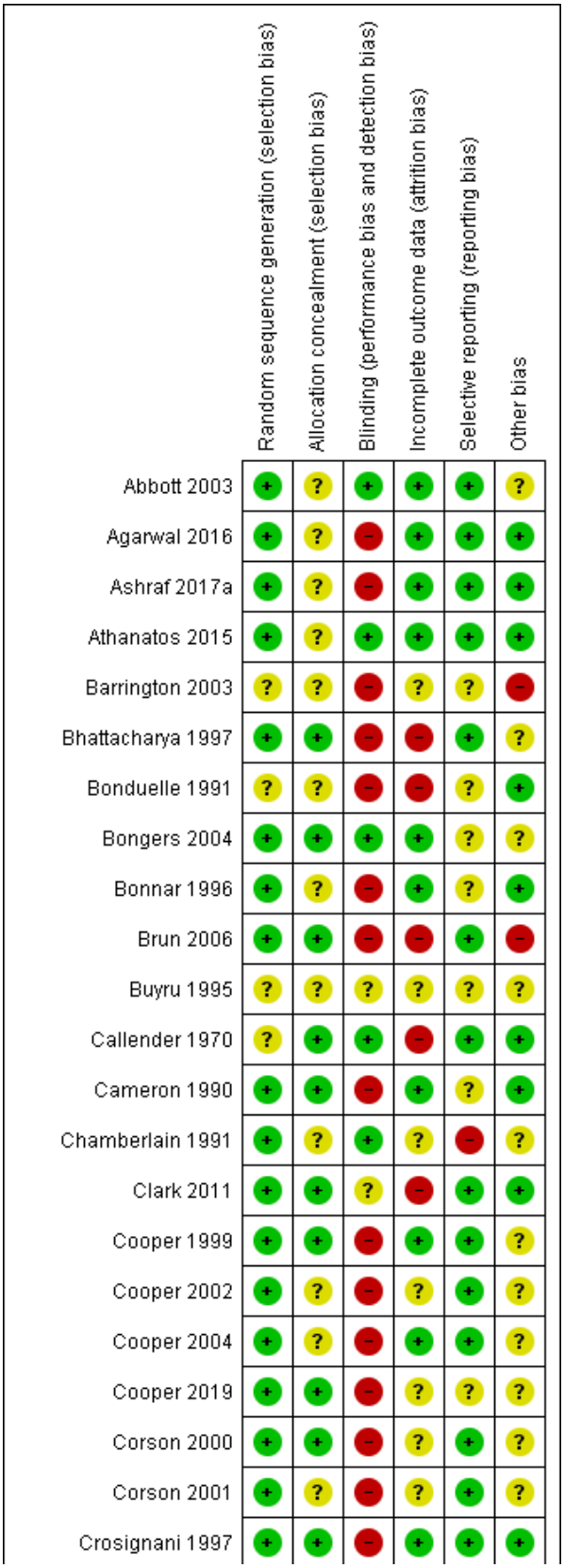


Figure 2. (Continued)

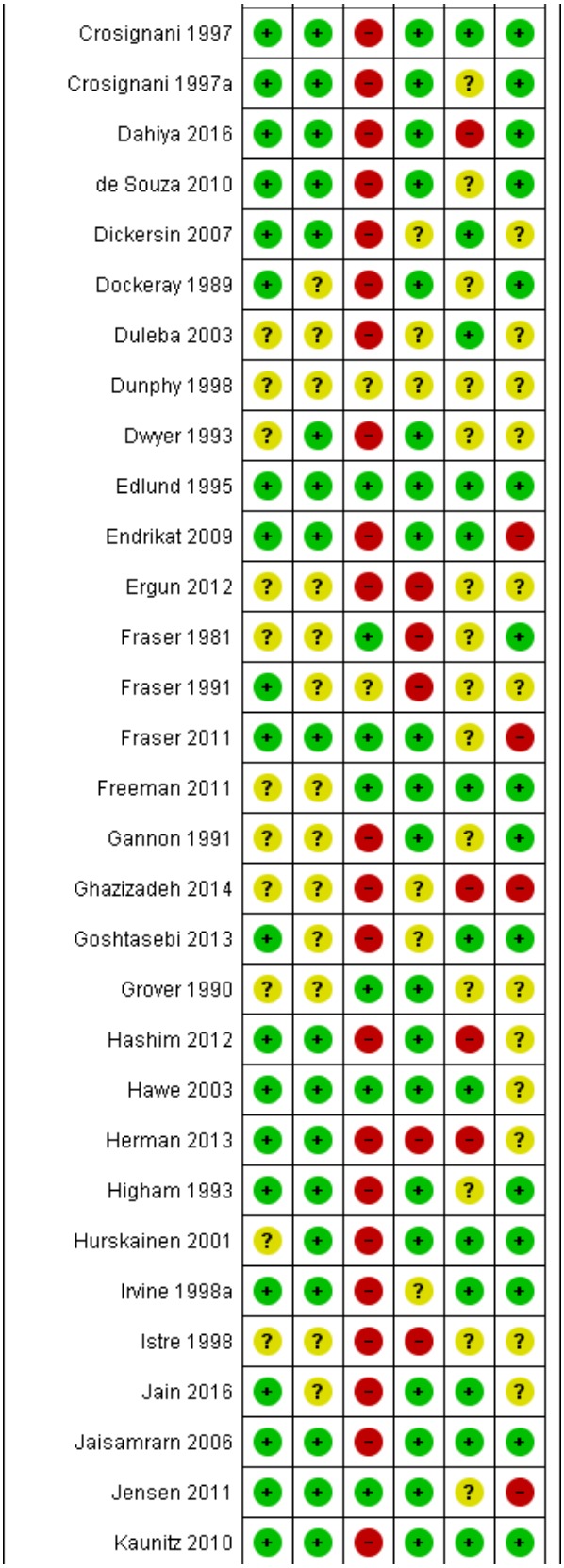


Figure 2. (Continued)

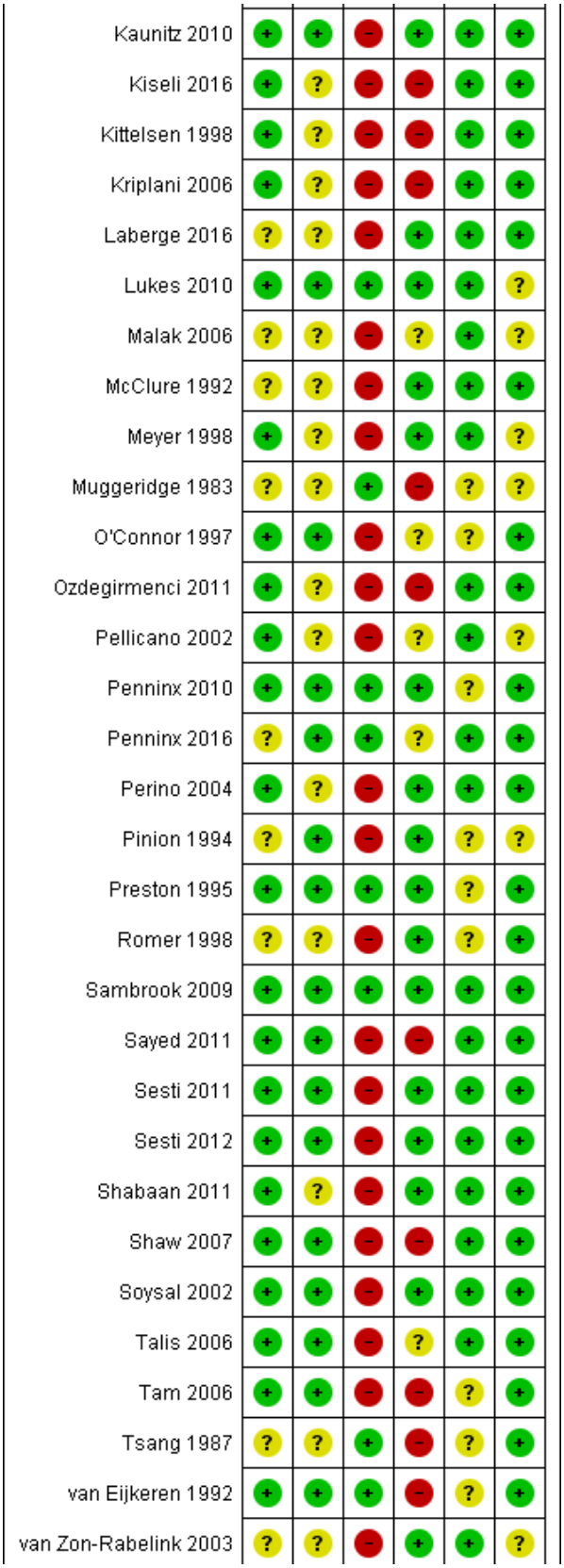


Figure 2. (Continued)

Our search for trials assessing the use of progestin-only contraceptives for HMB did not identify any available or ongoing clinical trials.

We excluded 11 HMB reviews. Ten had ineligible participants: in seven reviews women had HMB due to fibroids (Gupta 2014; Liu 2013; Murji 2017; Ping Liu 2013; Sangkomkamhang 2013; Song 2013; Tristan 2012), one related to anovulation (Hickey 2012), one to bleeding disorders (Ray 2016), and one to intrauterine devices (Grimes 2006). The last excluded review had an ineligible intervention – the use of preoperative endometrial thinning agents for women with HMB undergoing surgery (Tan 2013).

Methodological quality of included reviews

We used the AMSTAR 2 tool to rate the quality of the included reviews (Shea 2017). See Table 4 for details. A summary of the assessment is as follows.

1. All reviews included the components of participant, intervention, comparison and outcomes (PICO) in the research question and inclusion criteria.
2. All but Beaumont 2007 contained an explicit statement that the review methods were established prior to the conduct of the review, and the report justified if there was any significant deviations from the protocol.
3. All reviews included randomised controlled trials (RCTs). The authors based their methods on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).
4. In all but Beaumont 2007, authors reported using a comprehensive literature search strategy and included authors with subject-specific expertise.
5. Review authors reported performing study selection in duplicate in all reviews except Beaumont 2007.
6. Authors of all of the reviews reported performing data extraction in duplicate.
7. Authors of all of the reviews provided a list of excluded studies and justified the exclusions.
8. Authors of all of the reviews described the included studies in adequate detail.
9. Authors of all of the reviews used a satisfactory technique for assessing the risk of bias in individual studies that were included in the reviews. In Beaumont 2007 only allocation concealment was assessed, according to the *Cochrane Handbook* at that time.
10. Authors of all of the reviews reported on the sources of funding for the studies included in the reviews.
11. All of the reviews intended to perform a meta-analysis if suitable data were available. The review authors used appropriate statistical methods and based their methods on the *Cochrane Handbook*.
12. All but two of the reviews performed sensitivity analysis (Beaumont 2007; Bofill Rodriguez 2019b).
13. All but Beaumont 2007 described methods to take the risk of bias into account when interpreting and discussing the results of the review.
14. Authors of all of the reviews provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review.
15. All the reviews except Beaumont 2007 intended to investigate publication bias using methods described in the *Cochrane Handbook*.
16. Authors of all of the reviews reported any potential sources of conflict of interest.

We consider points 1 to 10 of the AMSTAR 2 to be the most important ones for this specific overview. By performing an NMA, we used data from individual trials and did not base the conclusions on the review's analysis.

The risk of bias of studies providing data for the overview is summarised in Figure 2.

Effect of interventions

First-line treatments

There were 10 first-line interventions compared: placebo, non-steroidal anti-inflammatory drugs (NSAIDs), antifibrinolytics (tranexamic acid), combined oral contraceptives (COC), combined vaginal ring (CVR), long-cycle oral progestogens, luteal phase oral progestogens, levonorgestrel-releasing intrauterine system (LNG-IUS), danazol and ethamsylate.

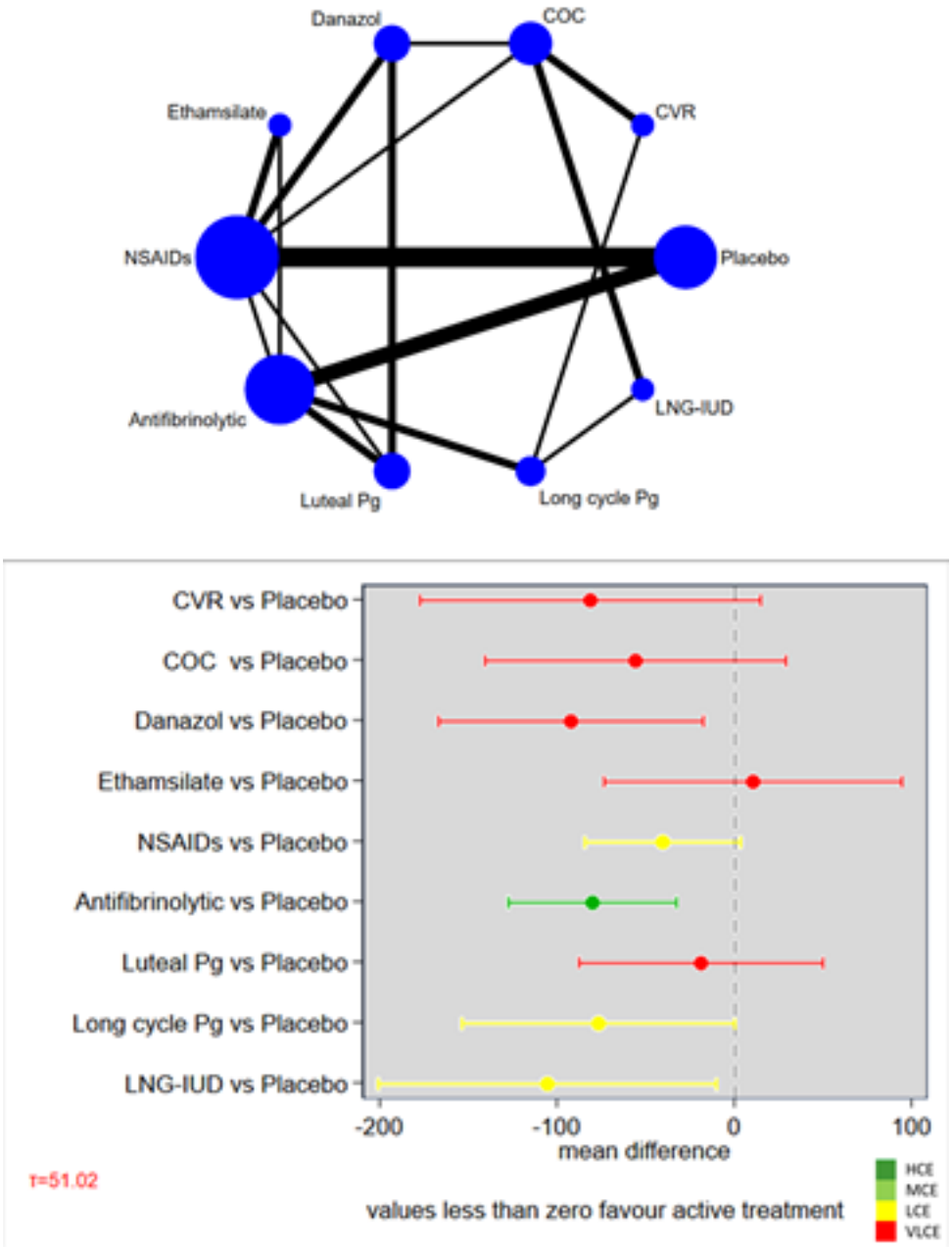
Primary outcomes

1. Menstrual blood loss reduction

Mean blood loss (combined)

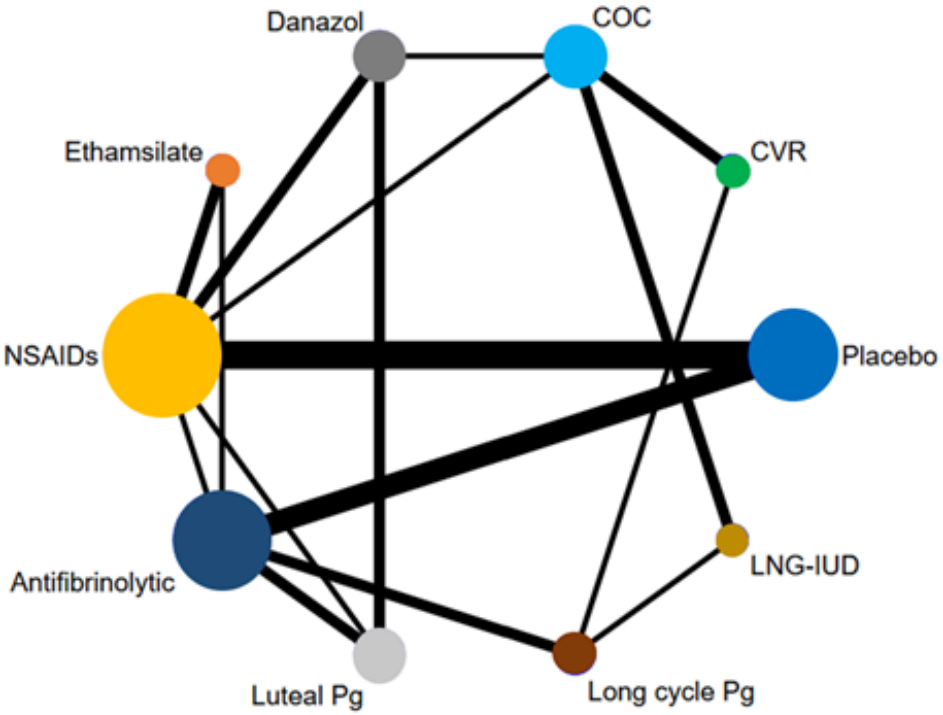
Twenty-six studies reported mean blood loss (either mean blood loss at the end of treatment or mean change from baseline), comparing all 10 treatments including placebo. See Table 5 for the summary of findings for this outcome.

Figure 73. The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison.



The network was connected; Figure 3 shows the NMA diagram for mean blood loss.

Figure 3. Network diagram for mean menstrual blood loss with first-line treatments (combined at the end of treatments and change from baseline) (26 studies, 10 treatments). The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison.



As there was substantial heterogeneity (Tau = 51.05), we used a random-effects model. There was no evidence of incoherence using the node-split or inconsistency model (P = 0.99 and increase in heterogeneity). See Appendix 3 for details.

See Figure 4 for the forest plot comparing all interventions to placebo.

Figure 4. Forest plot for menstrual blood loss (mean blood loss at the end of treatment and change from baseline) for first-line treatments. Colours of the lines are according to the certainty of the evidence: dark green, high certainty evidence (HCE); light green, moderate certainty evidence (MCE); yellow, low certainty evidence (LCE); and red, very low certainty evidence (VLCE).

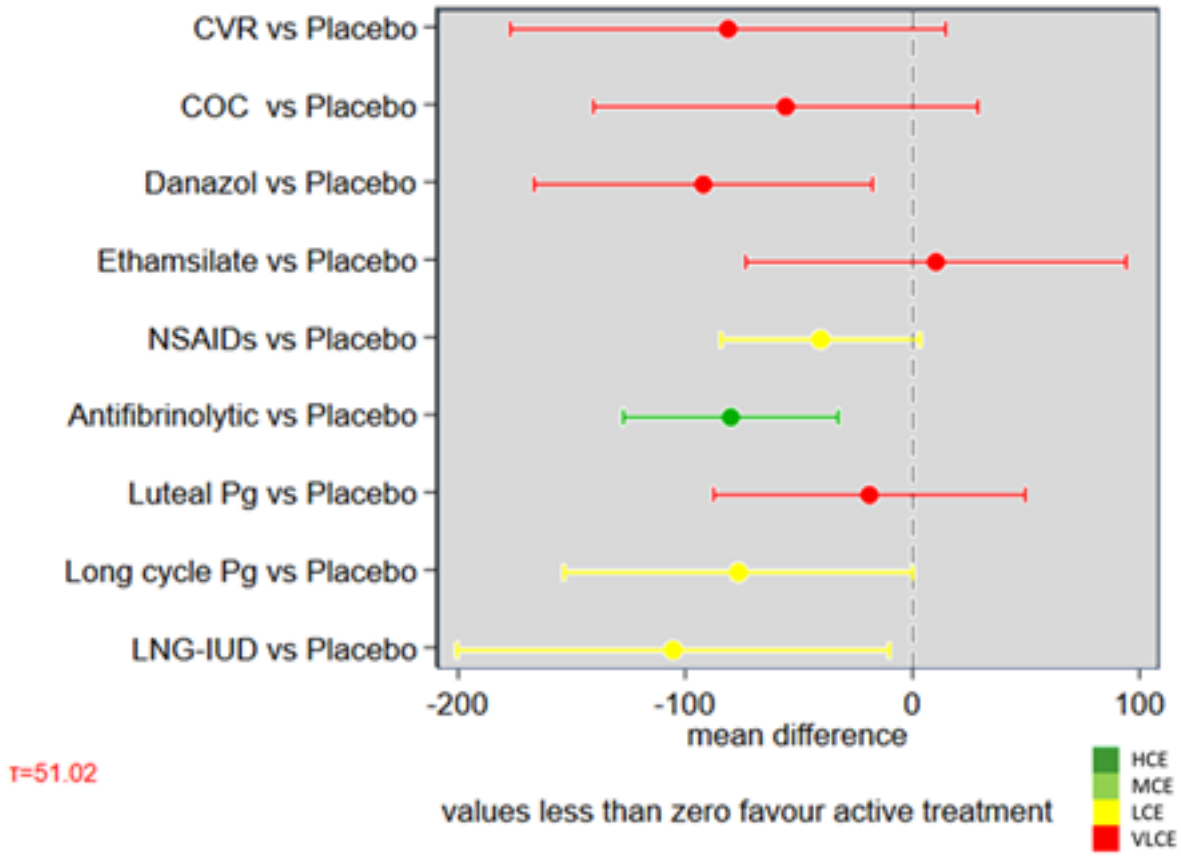
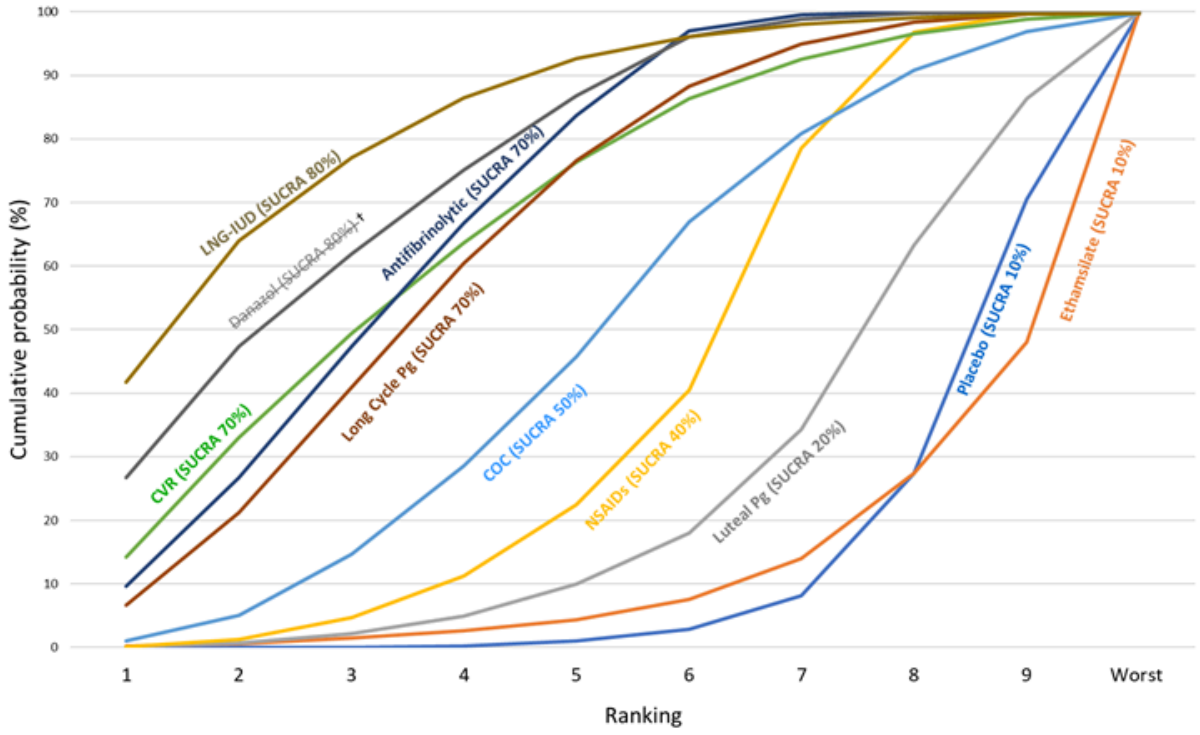


Figure 5 shows the cumulative probabilities for each treatment of being at each possible rank on reducing menstrual blood loss.

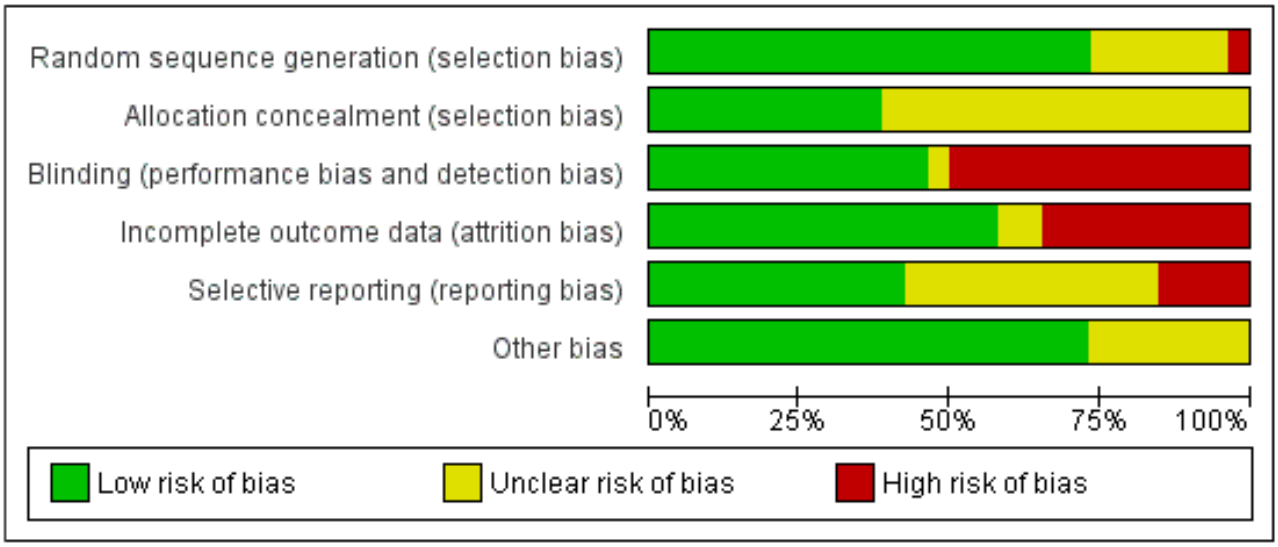
Figure 5. Cumulative rankogram comparing each treatment for menstrual blood loss (mean blood loss at the end of treatment and change from baseline) for first-line treatments. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface underneath the curve is a Cumulative Ranking line (SUCRA); the larger the SUCRA the higher its rank among all available treatments. Danazol (†): despite being effective in reducing menstrual bleeding, its adverse events advise against its use for heavy menstrual bleeding. Please refer to the last paragraph of the medical interventions in Description of the interventions.



- The best treatment for bleeding reduction was LNG-IUS (SUCRA 80%, mean rank 2.4, MD −105.71 mL/cycle, 95% CI −201.10 to −10.33; low certainty evidence).
- Second, danazol (†) (SUCRA 80%, mean rank 3.1, MD −92.43 mL/cycle, 95% CI −167.06 to −17.81; very low certainty evidence).
- Third, antifibrinolytics (SUCRA 70%, mean rank 3.7, MD −80.32 mL/cycle, 95% CI −127.67 to −32.98; moderate certainty evidence).
- Fourth, CVR (SUCRA 70%, mean rank 3.9, MD −81.53 mL/cycle, 95% CI −177.56 to 14.50; very low certainty evidence).
- Fifth, long-cycle cyclical progestogen (SUCRA 70%, mean rank 4.1, MD −76.93 mL/cycle, 95% CI −153.82 to −0.05; low certainty evidence).
- Sixth, combined oral contraceptives (COC) (SUCRA 50%, mean rank 5.7, MD −56.08 mL/cycle, 95% CI −140.88 to 28.72; very low certainty evidence).
- Seventh, NSAIDs (SUCRA 40%, mean rank 6.4, MD −40.67 mL/cycle, 95% CI −84.61 to 3.27; low certainty evidence).
- Eighth, cyclical luteal progestogen (SUCRA 20%, mean rank 7.8, MD −19.10 mL/cycle, 95% CI −87.81 to 49.61; very low certainty evidence).
- Ethamsylate and placebo were the worst treatments (SUCRA 10%, mean rank 8.9, MD 10.20 mL/cycle, 95% CI −73.73 to 94.12; very low certainty evidence, for ethamsylate; placebo (SUCRA 10%, mean rank 8.9 reference comparator).

Figure 6 summarises the risk of bias of individual trials contributing data to the NMA. Ninety-five per cent to 100% of the trials were either at low or unknown risk of selection bias (random sequence generation and allocation concealment) and other bias (such as baseline characteristics). Half were at high risk of performance and detection bias (blinding), probably because blinding is difficult due to different routes and timing of administration (COC is usually one pill daily, antifibrinolytics is only during the days of bleeding, the intrauterine system is inserted only once, the vaginal ring lasts for three weeks, etc.); The outcome is likely to be influenced by the lack of blinding. Forty per cent were at high risk of attrition (incomplete outcome data), and 20% were at high risk of reporting bias (selective reporting).

Figure 6. Risk of bias of trials contributing with data for menstrual blood loss (mean blood loss at the end of treatment and mean change from baseline) for first-line treatments.

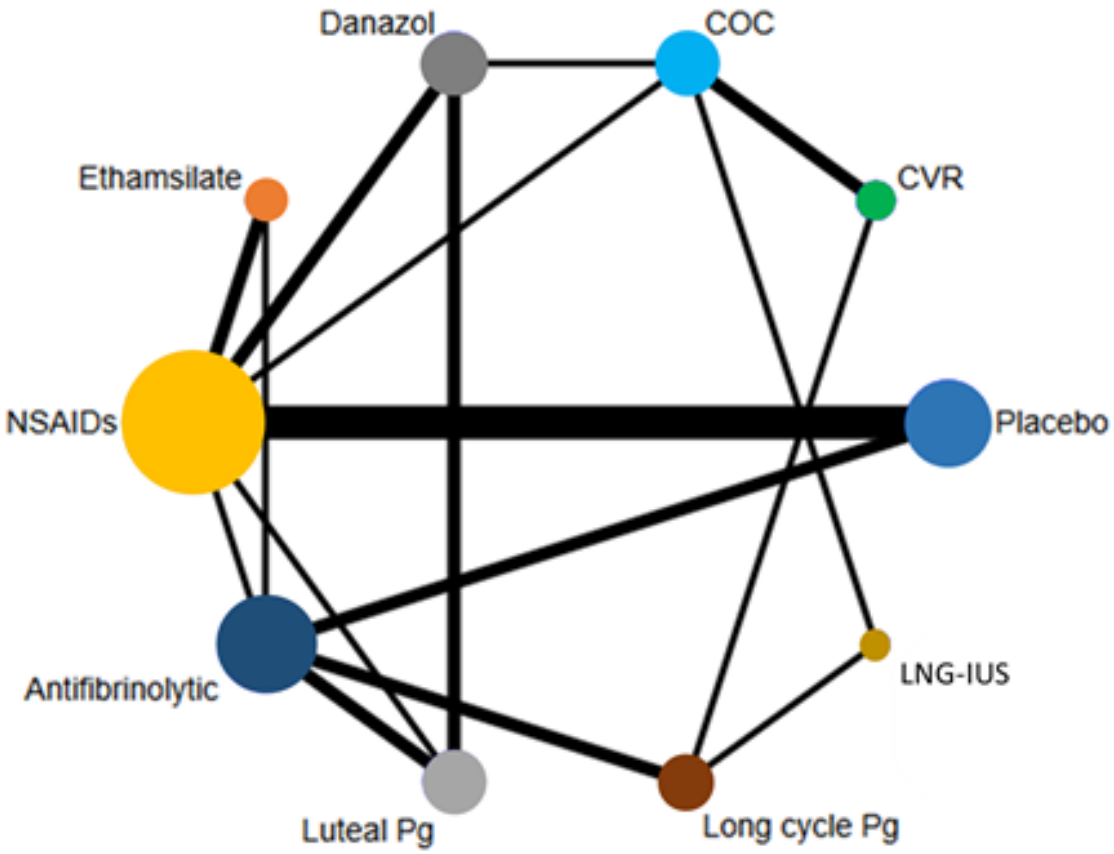


Sensitivity analysis for menstrual blood loss reduction

We performed a sensitivity analysis of the mean blood loss (excluding the change from baseline data). There were 23 studies. See Table 6 for summary of findings table for this outcome.

The network was connected. The NMA diagram is represented in Figure 7.

Figure 7. Network for menstrual blood loss mean blood loss at follow-up (23 studies, 10 treatments, sensitivity analysis) for first-line treatments.The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison.



We used a random-effects model (Tau = 32.6). The node-split model showed some evidence of incoherence (See Appendix 4 for details) in loops formed by CVR, COC, long-cycle progestogens and LNG-IUS. The inconsistency model gave a P value of 0.32, however, there was a reduction in heterogeneity (Tau = 27.66), suggesting some incoherence. In the presence of incoherence, results should be interpreted with caution.

See Figure 8 for the forest plot comparing all interventions to placebo.

Figure 8. Forest Plot for mean blood loss (sensitivity analysis) for first-line treatments. All the evidence has very low certainty.

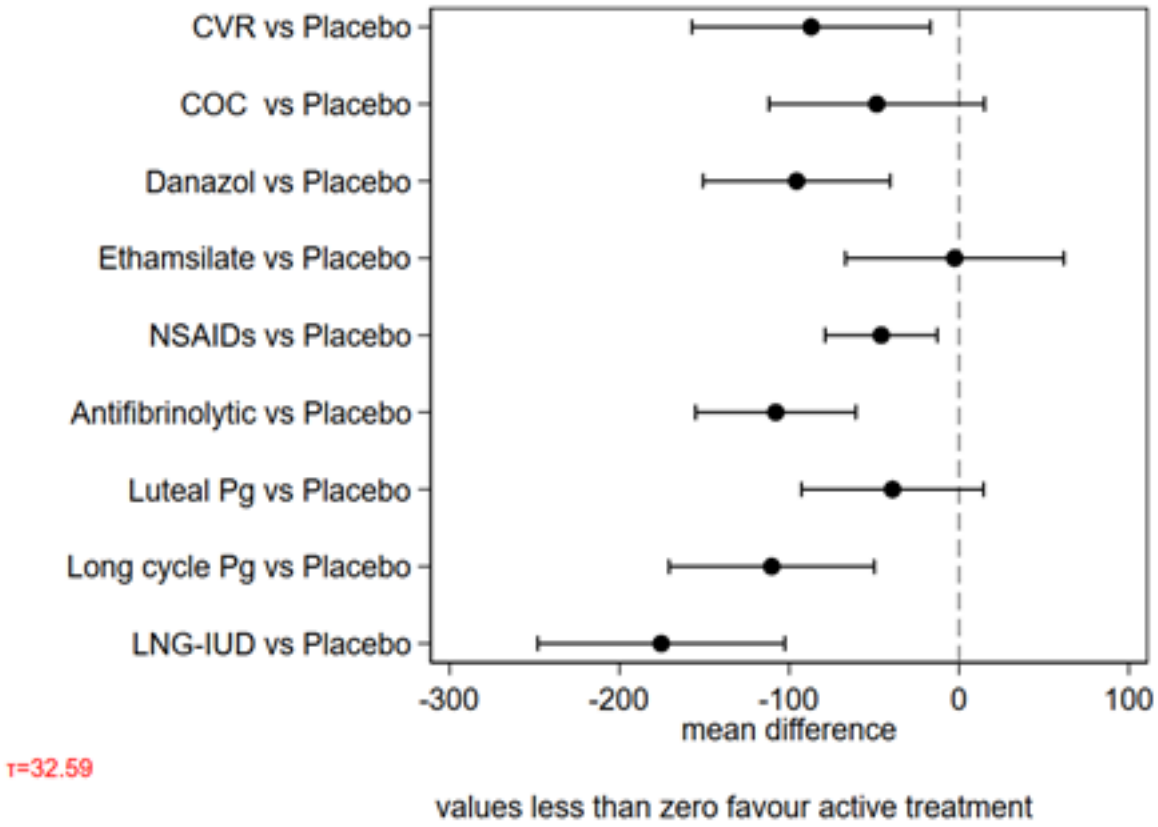
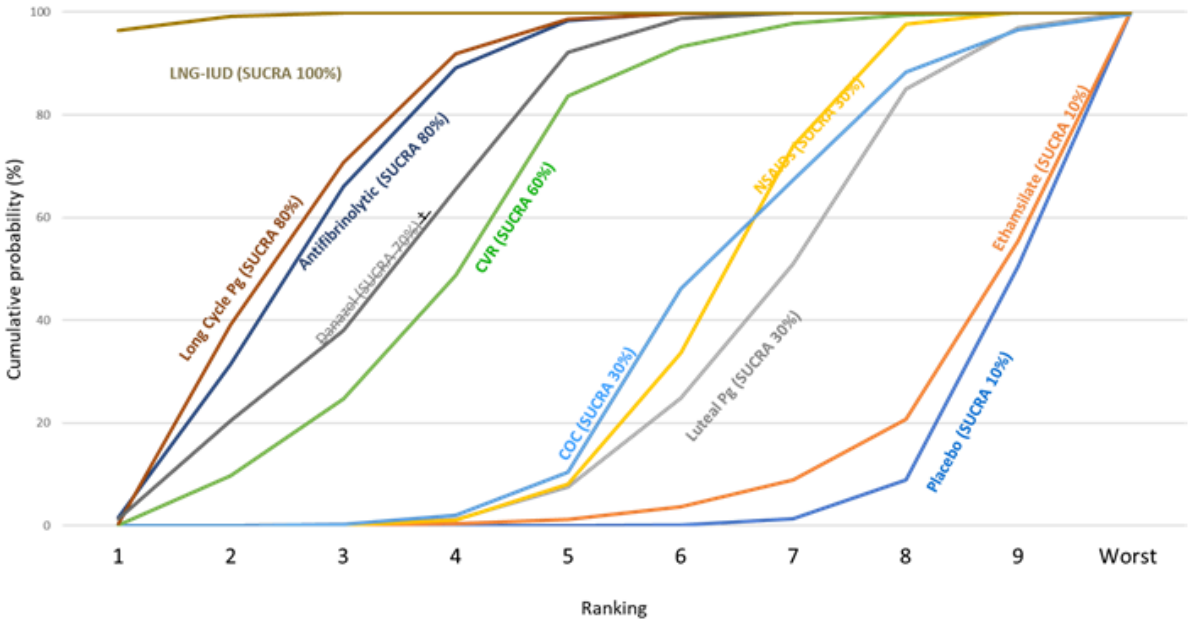


Figure 9 shows the cumulative probabilities for each treatment at each possible rank for reducing menstrual blood loss.

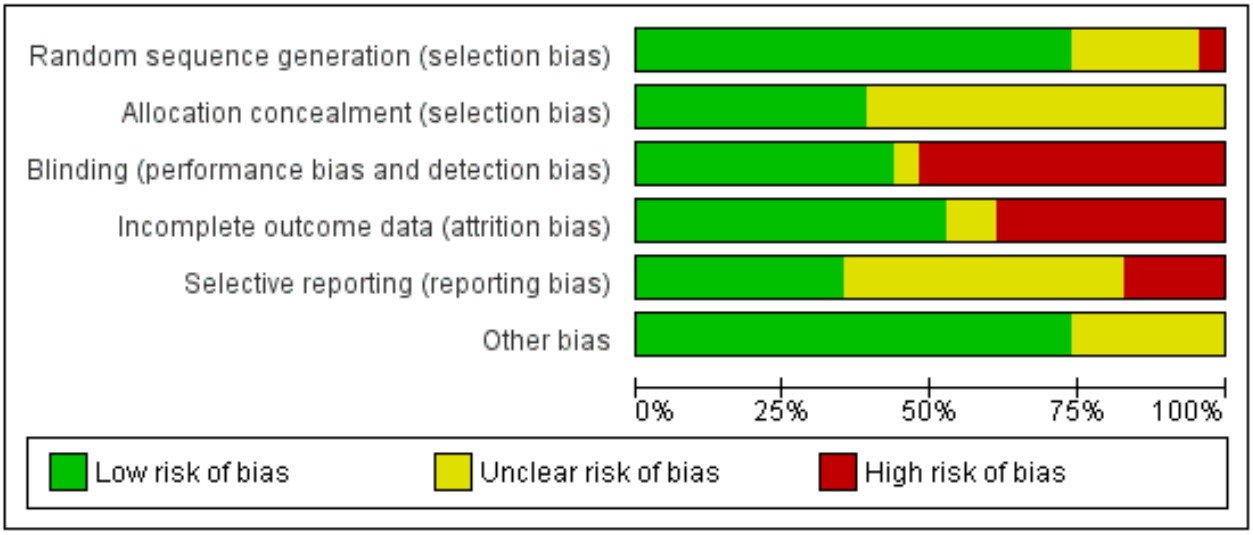
Figure 9. Cumulative rankogram comparing each treatment for mean blood loss at the end of treatment (sensitivity analysis) for first-line treatments. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface under the curve is a cumulative ranking line (SUCRA); the larger the SUCRA, the higher its rank among all available treatments. Danazol (†): despite being effective in reducing menstrual bleeding, its adverse events advise against its use for heavy menstrual bleeding. Please refer to the last paragraph of the medical interventions in Description of the interventions.



- The best treatment for reducing menstrual bleeding was LNG-IUS (SUCRA 100%, mean rank 1.0, MD −175.34 mL/cycle, 95% CI −248.09 to −102.58; very low certainty evidence).
- Second, long-cycle progestogen (SUCRA 80%, mean rank 3.0, MD −110.32 mL/cycle, 95% CI −170.75 to −49.9; very low certainty evidence).
- Third, antifibrinolytics (SUCRA 80%, mean rank 3.1, MD −107.93 mL/cycle, 95% CI −155.12 to −60.73; very low certainty evidence).
- Fourth, danazol (†) (SUCRA 70%, 3.8, MD −95.64 mL/cycle, 95% CI −150.71 to −40.56; very low certainty evidence).
- Fifth, CVR (SUCRA 60%, mean rank 4.4, MD −87.04 mL/cycle, 95% CI −157.23 to −16.86; very low certainty evidence).
- Sixth, COC and NSAIDs (both have SUCRA 30%, mean rank 6.9; COC: MD −48.48 mL/cycle, 95% CI −111.89 to 14.93; very low certainty evidence).
- Eight, cyclical luteal progestogen (SUCRA 30%, mean rank 7.3, MD −39.17 mL/cycle, 95% CI −92.76 to 14.41; very low certainty evidence).
- Ninth, ethamsylate (SUCRA 10%, mean rank 9.1, MD −2.56 mL/cycle, 95% CI −66.84 to 61.73; very low certainty evidence)
- Worst, placebo (SUCRA 10%, mean rank 9.4).

Figure 10 summarises the risk of bias of individual trials contributing data to the sensitivity NMA, and it is similar to the main analysis. There was a low or unknown risk of selection bias (random sequence generation and allocation concealment) in 95% of the trials, and of other bias (such as baseline characteristics) in 100%. Half were at high risk of performance and detection bias (blinding), 40% were at high risk of attrition bias (incomplete outcome data), and 20% were at high risk of reporting bias (selective reporting).

Figure 10. Risk of bias of trials contributing with data for mean blood loss at the end of treatment, sensitivity analysis, for first-line treatment.



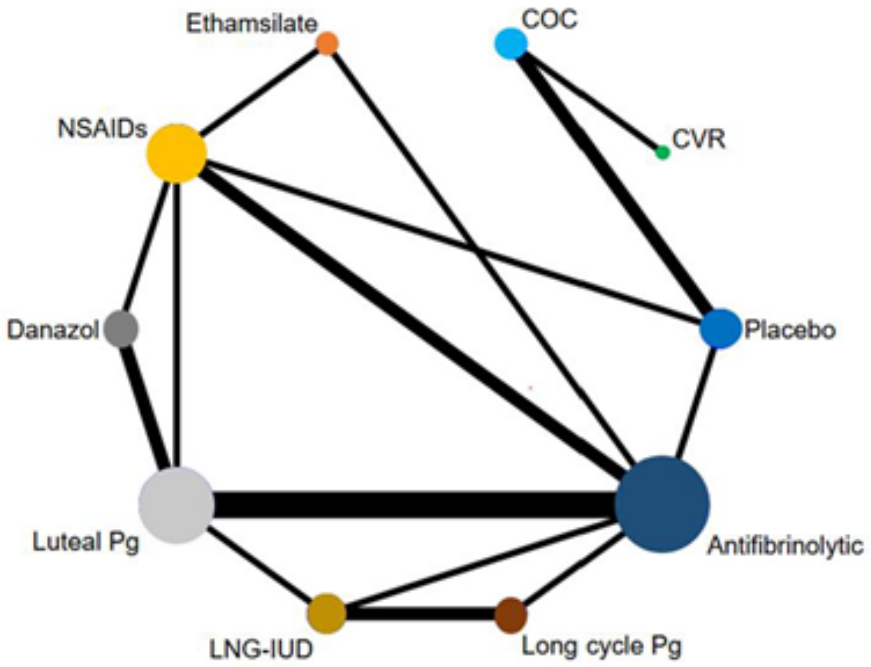
The sensitivity analysis removing imputed data resulted in very low certainty evidence, and we are uncertain of the effect of the interventions.

Perception of bleeding improvement

Sixteen studies reported patients' perception of bleeding improvement, comparing all 10 treatments. See Table 7 for the summary of findings table for this outcome.

The network was connected; the NMA diagram for mean blood loss is represented in Figure 11.

Figure 11. Network for women with perception of improvement for first-line treatments (16 studies, 10 treatments). The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison.



We used a random-effects model (Tau = 1.03). The node-split model showed some evidence of incoherence (see Appendix 5 for details) in loops formed by NSAIDs, antifibrinolytics and LNG-IUS. The inconsistency model gave a P value of 0.003, and there was a reduction in heterogeneity (Tau = 0.39), suggesting incoherence. In the presence of incoherence, results should be interpreted with caution.

See Figure 12 for the forest plot comparing all interventions to placebo.

Figure 12. Forest plot for perception of bleeding improvement forfirst-line treatments. All evidence has very low certainty.

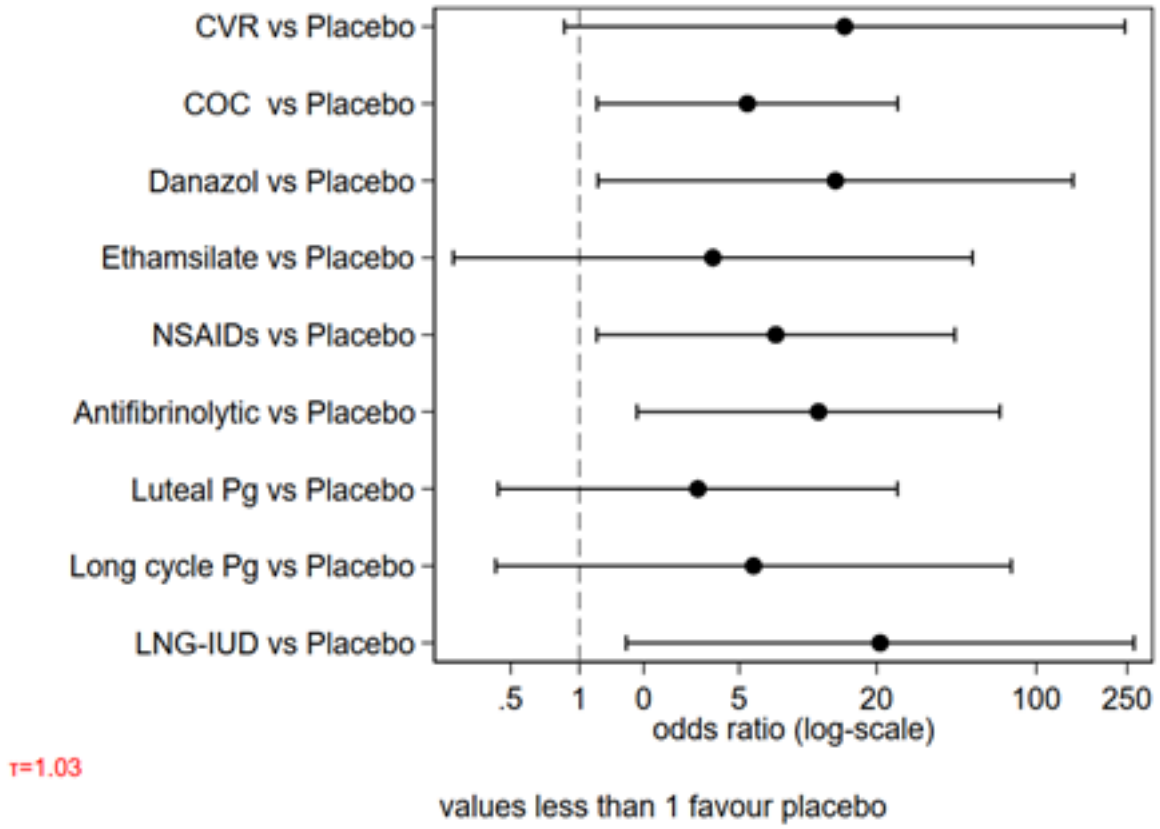
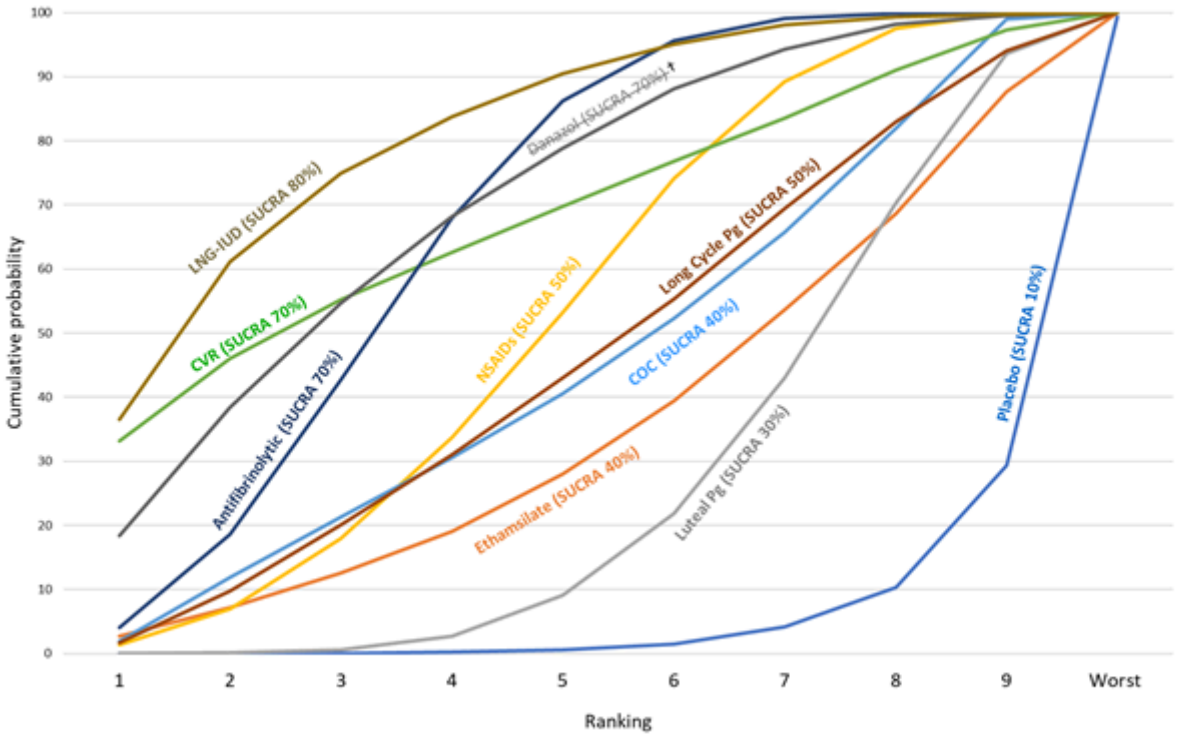


Figure 13 shows the cumulative probabilities for each treatment at each possible rank for reducing menstrual blood loss.

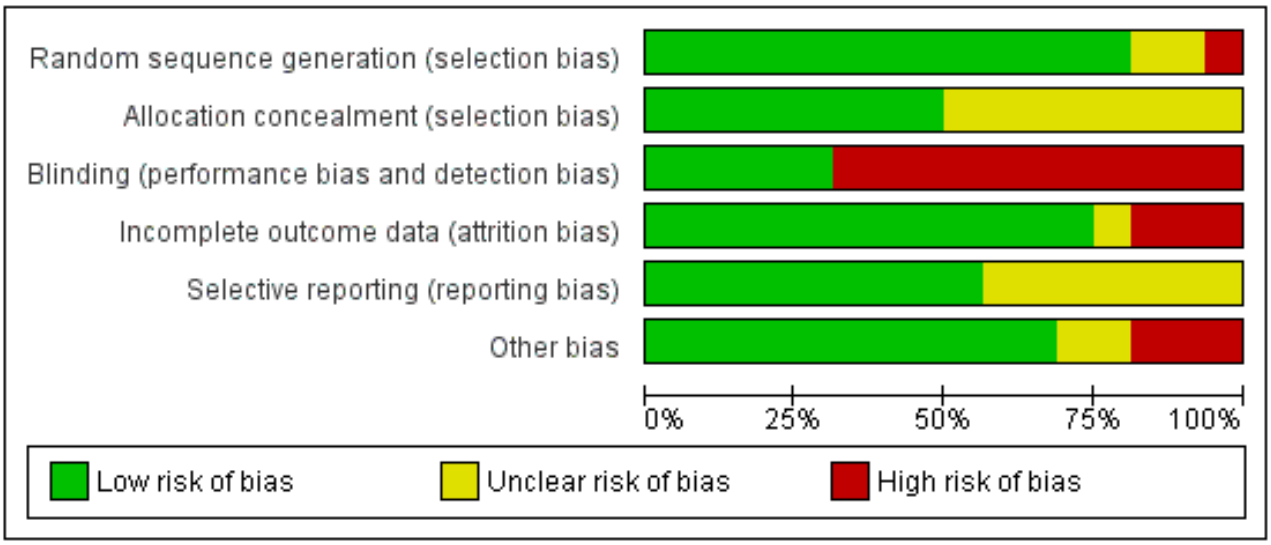
Figure 13. Cumulative rankogram comparing each treatment for perception of improvement forfirst-line treatments. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface under the curve is a cumulative ranking line (SUCRA); the larger the SUCRA the higher its rank among all available treatments. Danazol (†): despite being effective in reducing menstrual bleeding, its adverse events advise against its use for heavy menstrual bleeding. Please refer to the last paragraph of the medical interventions in Description of the interventions.



- The best HMB treatment in terms of perception of improvement was LNG-IUS (SUCRA 80%, mean rank 2.6, OR 20.73, 95% CI 1.60 to 267.83; very low certainty evidence).
- Second, danazol (†) (SUCRA 70%, mean rank 3.6, OR 20.73, 95% CI 1.60 to 267.84; very low certainty evidence).
- Third, CVR (SUCRA 70%, mean rank 3.8, OR 14.49, 95% CI 0.86 to 244.30; very low certainty evidence).
- Fourth, antifibrinolytics (SUCRA 70%, mean rank 3.9, OR 11.13, 95% CI 1.79 to 69.30; very low certainty evidence).
- Fifth, NSAIDs (SUCRA 50%, mean rank 5.3, OR 7.24, 95% CI 1.19 to 44.01; very low certainty evidence).
- Sixth, long-cycle progestogens (SUCRA 50%, mean rank 5.9, OR 5.78, 95% CI 0.43 to 77.71; very low certainty evidence).
- Seventh, COC (SUCRA 40%, mean rank 6.0, OR 5.43, 95% CI 1.19 to 24.73; very low certainty evidence).
- Eighth, ethamsylate (SUCRA 40%, mean mean rank 6.8, OR 3.84, 95% CI 0.28 to 52.54; very low certainty evidence).
- Nineth, luteal progestogen (SUCRA 30%, mean rank 7.6, OR 3.30, 95% CI 0.44 to 24.68; very low certainty evidence).
- Worst, placebo (SUCRA 10%, mean mean rank 9.5).

Figure 14 summarises the risk of bias of individual trials contributing data to the NMA. Over 90% were at either low or unknown risk of selection bias (random sequence generation and allocation concealment) and other bias (such as baseline characteristics). Over 70% were at high risk of performance and detection bias (blinding), so the outcome is likely to be influenced by the lack of blinding. Eighty per cent were at low or unclear risk of attrition bias (incomplete outcome data), and 100% were at low or unclear risk of reporting bias (selective reporting).

Figure 14. Risk of bias of trials contributing with data to proportion of women with perception of improvement for first-line treatment.

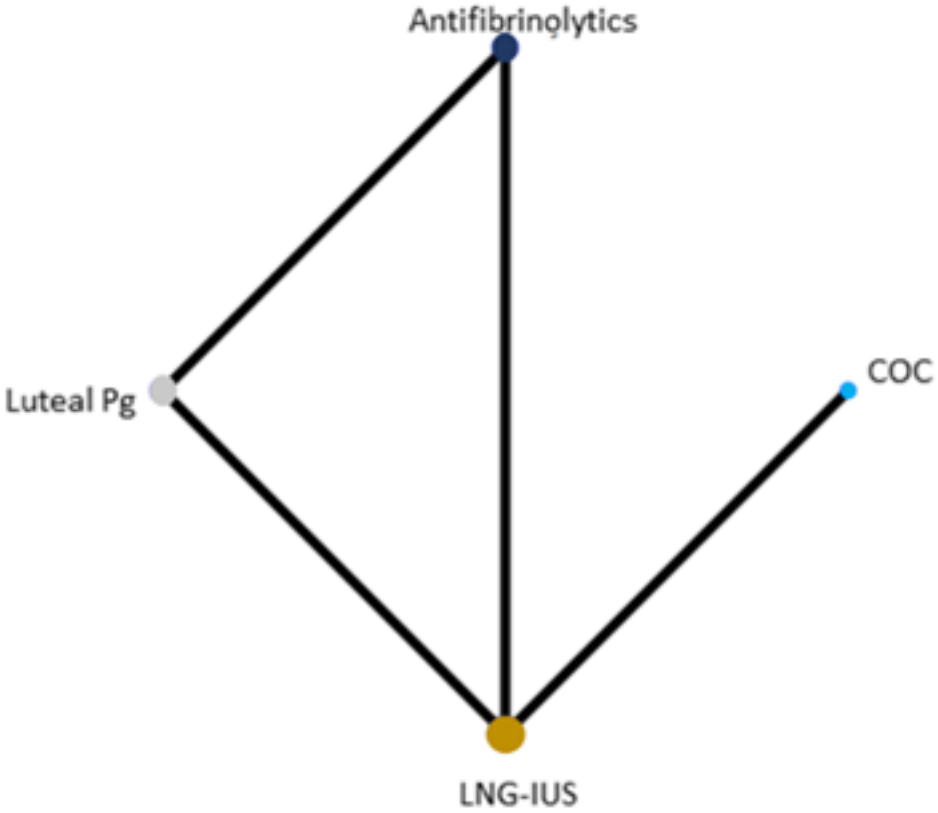


2. Satisfaction

Three studies with six treatments reported satisfaction, although only two studies with four interventions (antifibrinolytics, COC, luteal progestogens and LNG-IUS) were in a connected network. See Table 8 for the summary of findings table for this outcome.

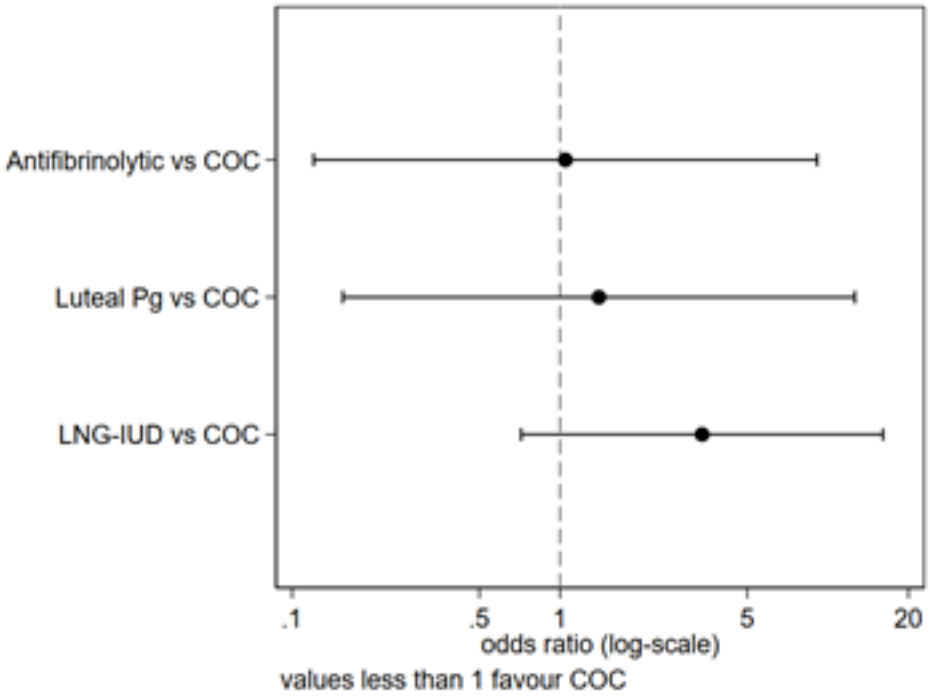
The analysis was done on the connected subnetwork; see Figure 15. As there is only a single study per comparison, we used a fixed-effect model.

Figure 15. Network for satisfaction for first-line treatments (2 studies, 4 treatments).The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison.



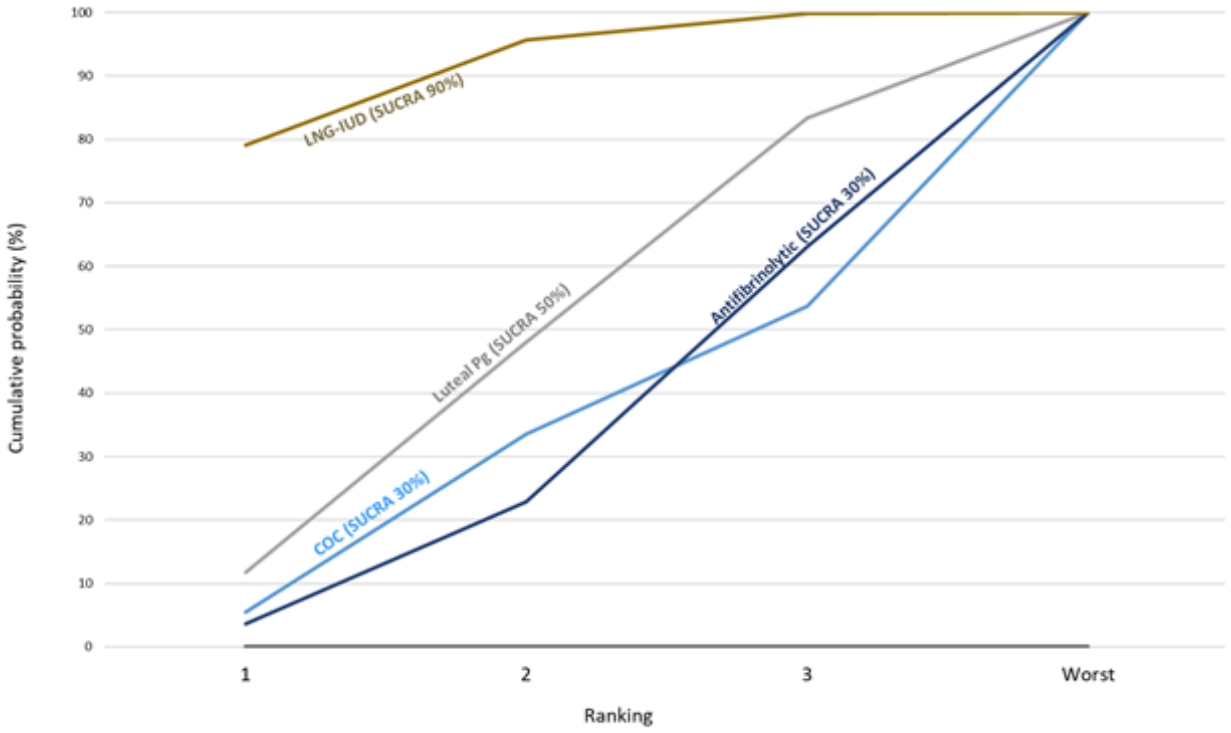
See Figure 16 for the forest plot. We are uncertain of the true effect of antifibrinolytics, luteal progestogens, LNG-IUS and COC for satisfaction (all very low certainty evidence).

Figure 16. Forest plot for satisfaction with first-line treatments All evidence has very low certainty.



We used COC as a comparator, as there were no studies assessing satisfaction using placebo as a comparator. Figure 17 presents the cumulative probabilities for each treatment at each possible rank in terms of satisfaction compared to COC (cumulative SUCRA).

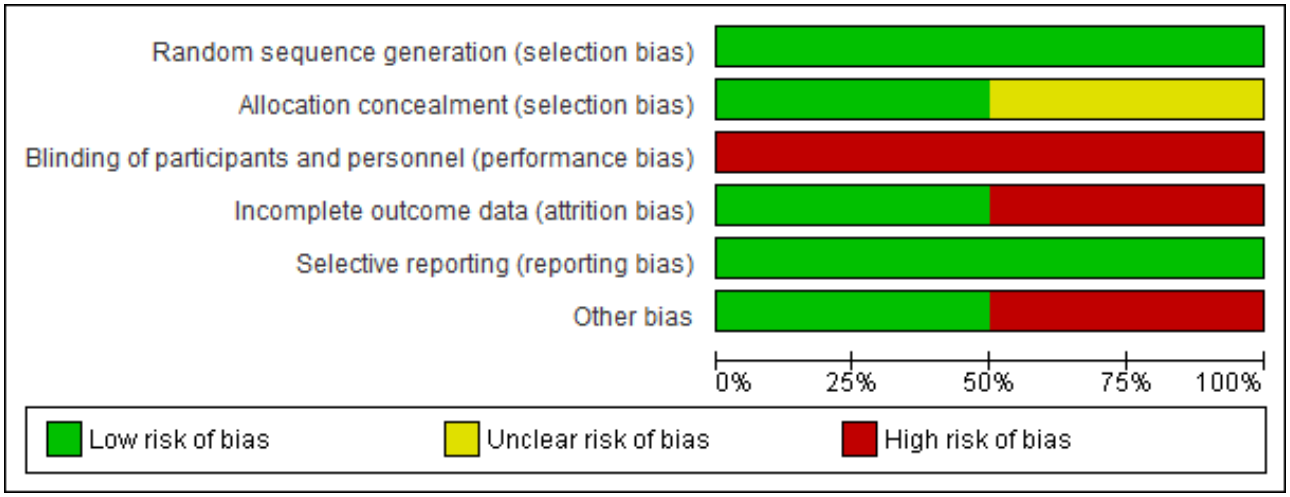
Figure 17. Cumulative rankogram comparing each treatment for satisfaction forfirst-line treatments. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface under the curve is a cumulative ranking line (SUCRA); the larger the SUCRA the higher its rank among all available treatments.



- Best, LNG-IUS (SUCRA 90%, mean rank 1.3, OR 3.39, 95% CI 0.72 to 16.07; very low certainty evidence).
- Second, luteal progestogen (SUCRA 50%, mean rank 2.6, OR 1.39, 95% CI 0.15 to 12.61; very low certainty evidence).
- Third, antifibrinolytics (SUCRA 30%, mean rank 3.1, OR 1.05, 95% CI 0.12 to 9.12; very low certainty evidence) and COC (SUCRA 30%, mean rank 3.1).

Figure 18 summarises the risk of bias of the trials contributing data to the NMA. All were at low or unknown risk of selection and reporting bias. Half were at high risk of attrition and other bias. All were at high risk of performance and detection bias, as blinding is very unlikely among these interventions, and knowing the intervention is likely to interfere with the satisfaction.

Figure 18. Risk of bias of studies included on the network for satisfaction for first-line treatments.



Secondary outcomes

1. Quality of life

Data extracted were not suitable to combine in an NMA because they were reported as mean differences (with an SD) measured on different scales, and this was not enough to calculate an SMD. It was therefore inappropriate to pool results. Using standardised means, there was extremely high inconsistency in the NMA. We present the results from pairwise comparisons. See Table 9 for the summary of findings table for this outcome.

Antifibrinolytics versus long-cycle progestogen

Bryant-Smith 2018 reported there may be little to no difference in quality of life, measured with the SF-36 general health domain, when comparing antifibrinolytics (tranexamic acid) with long-cycle progestogen (medroxyprogesterone acetate; MD 5.00 points, 95% CI −2.49 to 12.49; 1 RCT, 90 women; low certainty evidence).

Antifibrinolytics versus short-cycle progestogen

Bryant-Smith 2018 reported that the evidence is uncertain regarding any differences in quality of life, measured by the proportion of women reporting an improvement, when comparing antifibrinolytics (tranexamic acid) with short-cycle progestogen (norethisterone) (RR 1.67, 95% CI 0.76 to 3.64; 1 RCT, 44 women; very low certainty evidence).

Levonorgestrel-releasing intrauterine-device (LNG-IUS) versus combined oral contraceptives (COC)

Bofill Rodriguez 2020 reported there may be little to no difference in quality of life, measured by the proportion of women reporting good or excellent quality of life, when comparing LNG-IUS to combined oral contraceptives (RR 1.20, 95% CI 0.72 to 2.00; $I^2 = 0$; 2 RCTs, 170 women; low certainty evidence).

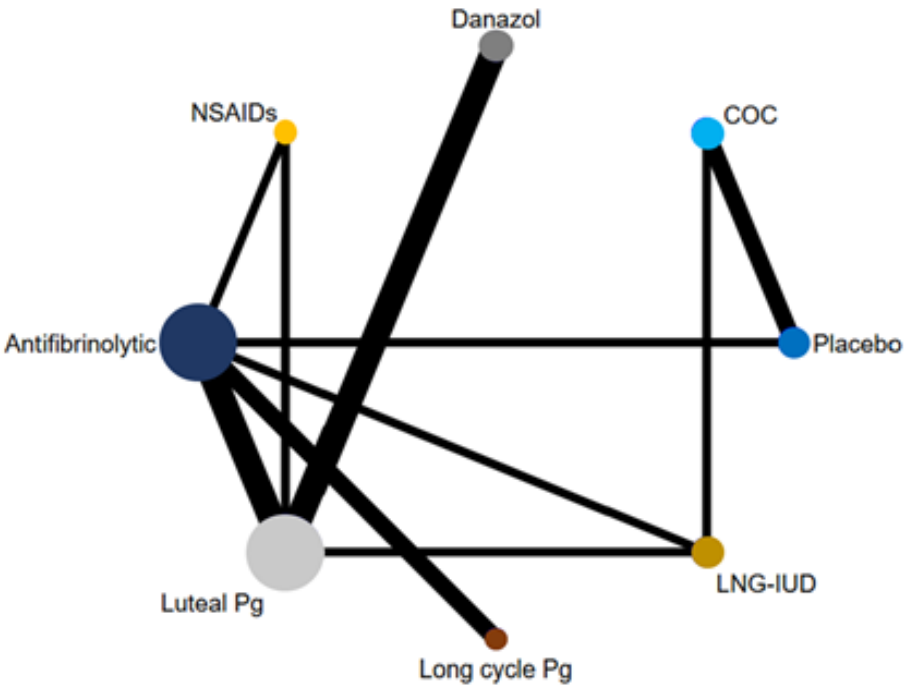
2. Adverse events

Adverse events for first-line treatments were reported mainly as individual side effects, and trials reported a wide variety, such as acne; anaemia; anxiety; arthralgia; back, chest and breast pain; breast tenderness; cervical dysplasia; depression; dizziness; dysmenorrhoea; dyspepsia; fatigue; headache; hypertension; insomnia; intermenstrual bleeding; leukorrhoea; metrorrhagia; migraine; nausea; vaginitis; voice and skin changes; and weight gain and loss. The abundance of adverse effects makes it impossible to combine due to the risk of double counting. Two trials comparing COC to placebo reported over 15 specific adverse events ((D) Fraser 2011; (D) Jensen 2011); although there was clear evidence of a difference favouring placebo for any adverse event, the only specific adverse events with clear evidence of difference was breast pain and metrorrhagia.

Fourteen studies reported 'any adverse events', comparing eight interventions: placebo, NSAIDs, antifibrinolytics (tranexamic acid), COCs, long-cycle and luteal oral progestogens, the LNG-IUS and danazol. See Table 10 for the summary of findings table for this outcome.

The network was connected; Figure 19 presents the NMA diagram for any adverse event.

Figure 19. Network diagram for any adverse events withfirst-line treatments (combined at the end of treatments and change from baseline) (26 studies 26, 10 treatments). The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison.



We used a fixed-effect model. There is no evidence of inconsistency using the node-split or inconsistency models (P value for inconsistency model 0.35). See details in Appendix 6.

See Figure 20 for the forest plot comparing all interventions to placebo for any side effects. Figure 21 shows the cumulative probabilities for each treatment at each possible rank in terms of adverse events.

Figure 20. First-line treatments. Forest plot any adverse event. Colours of the lines are according to the certainty of the evidence: dark green, high certainty evidence (HCE); light green, moderate certainty evidence (MCE); yellow, low certainty evidence (LCE); and red, very low certainty evidence (VLCE).

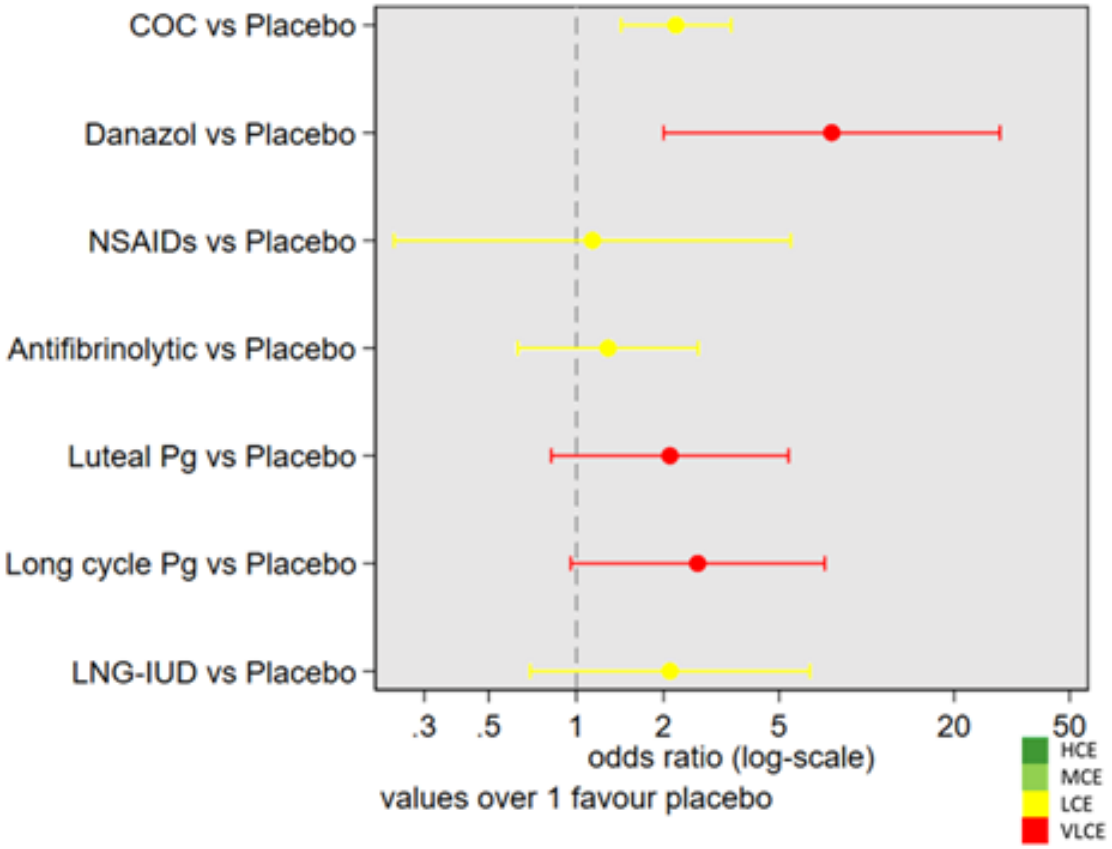
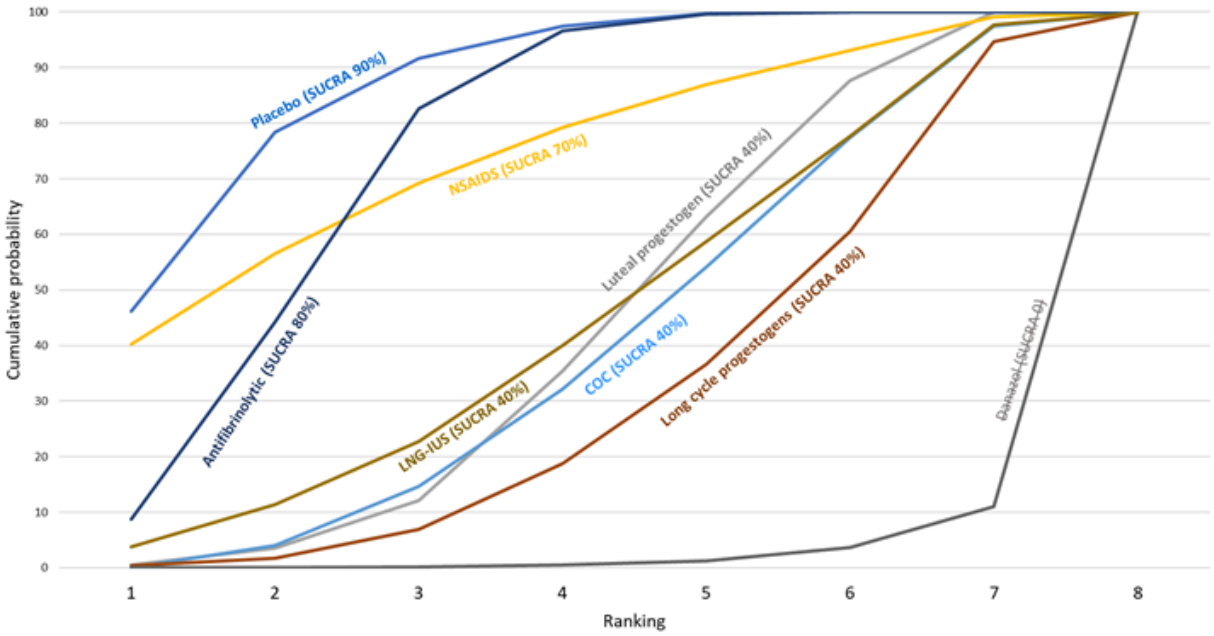


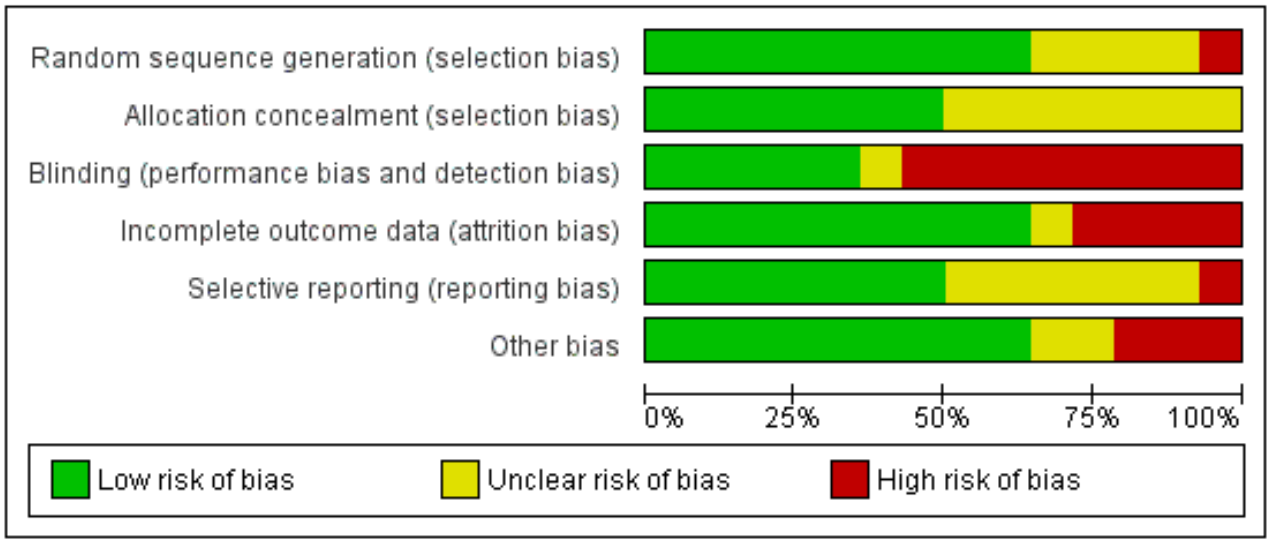
Figure 21. Cumulative rankogram comparing each treatment for any adverse events withfirst-line treatments. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface underneath the curve is a cumulative ranking line (SUCRA); the larger the SUCRA the higher its rank among all available treatments. Danazol (†): despite being effective in reducing menstrual bleeding, its adverse events advise against its use for heavy menstrual bleeding. Please refer to the last paragraph of the medical interventions in Description of the interventions.



- The best HMB treatment in terms of adverse events was placebo (SUCRA 90%, mean rank 1.9, reference comparator).
- Second, antifibrinolytics (SUCRA 80%, mean rank 2.7, OR 1.29, 95% CI 0.63 to 2.63; low certainty evidence).
- Third, NSAIDs (SUCRA 70%, mean rank 2.8, OR 1.14, 95% CI 0.24 to 5.48; low certainty evidence).
- Fourth, LNG-IUS (SUCRA 40%, mean rank 4.9, OR 2.10, 95% CI 0.69 to 6.38; low certainty evidence).
- Fifth, luteal progestogens (SUCRA 40%, mean rank 5.0, OR 2.10, 95% CI 0.82 to 5.38; very low certainty evidence).
- Sixth, COC (SUCRA 40% mean rank 5.2, OR 2.21, 95% CI 1.43 to 3.41; very low certainty evidence).
- Seventh, long-cycle progestogens (SUCRA 30%, mean rank 5.8, OR 2.62, 95% CI 0.96 to 7.17; very low certainty evidence).
- Worst, danazol (SUCRA 0, mean rank 7.8, OR 7.58, 95% CI 2 to 28.75; very low certainty evidence).

Figure 22 summarises the risk of bias of individual trials contributing data to the NMA. Ninety per cent of trials were at either low or unknown risk of selection bias, 100% were at low or unknown risk of allocation concealment. Over 50% were at high risk of performance and detection bias due to lack of blinding, and over 80% were at low or unknown risk of selective reporting and other bias.

Figure 22. Risk of bias of studies included on the network for any adverse event for first-line treatments.



Severe adverse events

Severe adverse events were reported in only one trial comparing antifibrinolytics versus placebo (Table 11).

Bryant-Smith 2018 reported that there is probably little to no difference in the presence of serious adverse events (thrombosis) in women receiving antifibrinolytics versus placebo (RR 0.10, 95% CI 0.00 to 2.46, 2 RCTs, 468 women; moderate certainty evidence).

3. Requirement of additional medical treatment

The intrauterine device system review reported on the outcome of requirement of additional medical treatment in combination with treatment failure (Bofill Rodriguez 2020). Four studies reported failure related to a PBAC cutoff. Two studies, comparing COC and LNG-IUS, defined treatment failure as requirement of further treatment. See Table 12 for the summary of findings table for this outcome.

Levonorgestrel-releasing intrauterine-device (LNG-IUS) versus combined oral contraceptives (COC)

Bofill Rodriguez 2020 reported that evidence suggests that women using LNG-IUS are less likely to require further treatment due to treatment failure than women using COC (results from pairwise meta-analysis: RR 0.43, 95% CI 0.24 to 0.79; I^2 = 0%; 2 RCTs, 208 women; low certainty evidence).

Second-line treatments

Primary outcomes

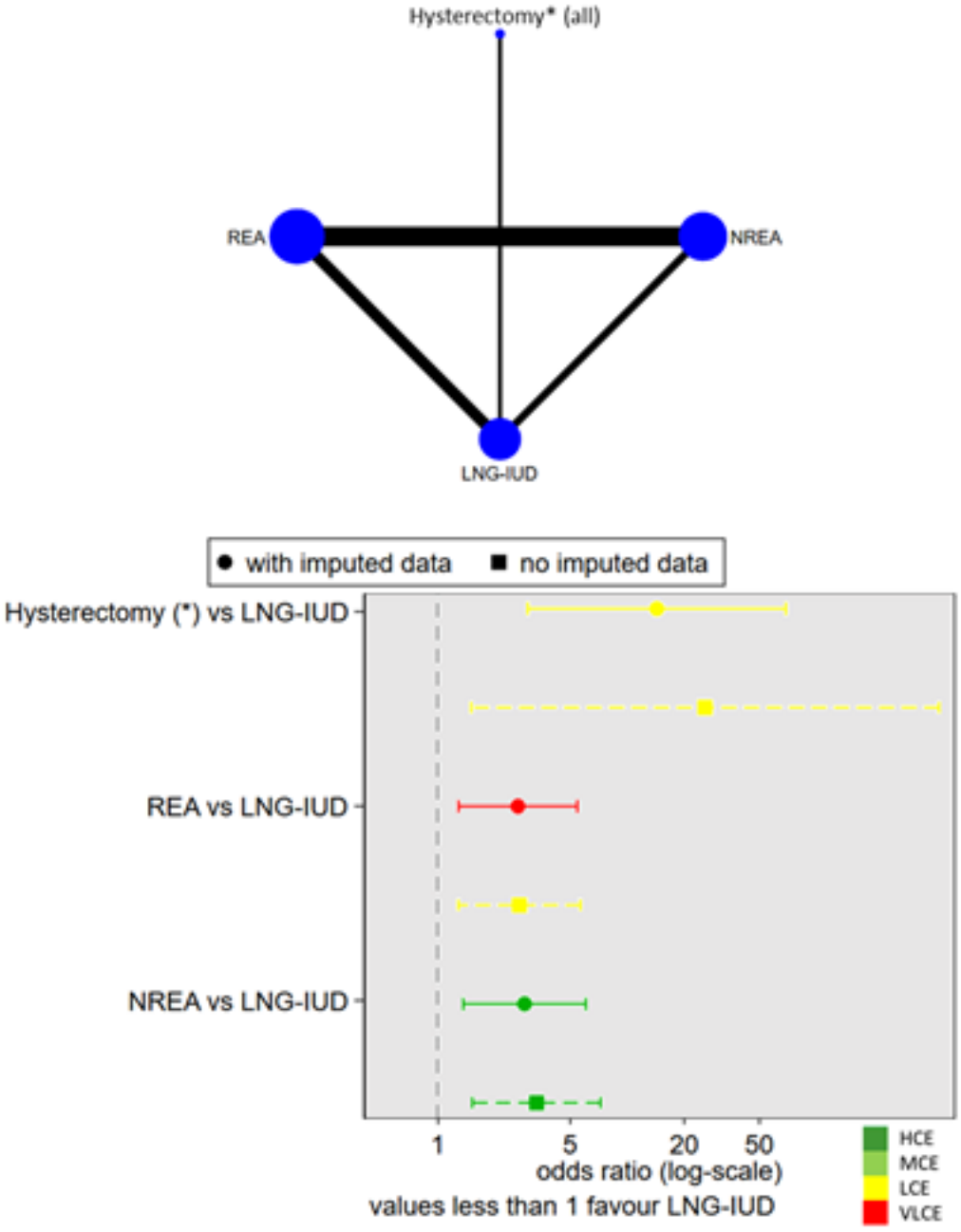
1. Menstrual blood loss reduction

For this outcome, we grouped all hysterectomy routes into a single intervention (hysterectomy).

Bleeding improvement

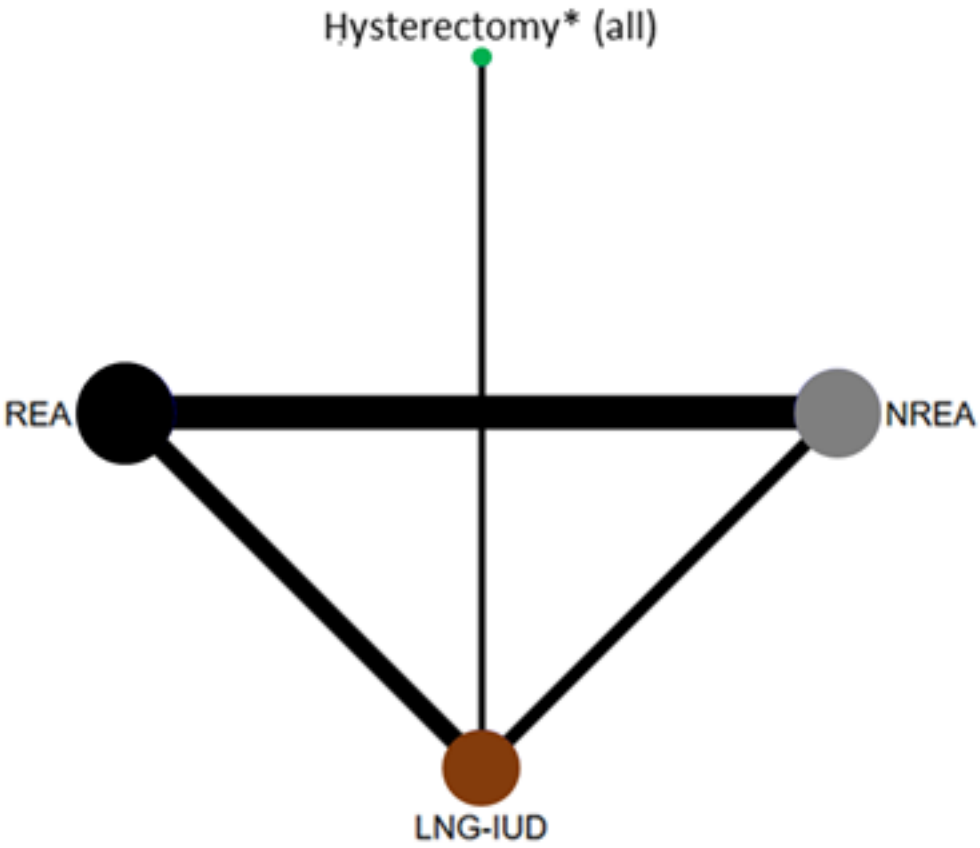
Eleven studies reported the proportion of women with bleeding improvement (PBAC under 75 points or acceptable bleeding improvement) at one year follow-up, comparing four interventions: LNG-IUS, REA, NREA and hysterectomy. See Table 13 for the summary of findings table for this outcome.

Figure 74. The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison.



The network is connected: Figure 23 presents the NMA diagram for PBAC improvement.

Figure 23. Network for bleeding (PBAC) improvement (no imputed data) for second-line treatments (11 studies, 4 treatments). The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Multiarm trials contribute to more than one comparison.



We used the fixed-effect model as the estimated Tau value was practically zero. There is no evidence of inconsistency using the node-split or inconsistency models (P value for inconsistency model 0.15). See consistency details in Appendix 7.

See Figure 24 for the forest plot. Figure 25 shows the cumulative probabilities for each treatment at each possible rank for improving the PBAC. Treatment hierarchies are presented with the surface under the cumulative curve (SUCRA) and mean rank (one to four).

Figure 24. Forest plot bleeding (PBAC) reduction forsecond-line treatments. With and without imputed data. Colours of the lines are according to the certainty of the evidence: dark green, high certainty evidence (HCE); light green, moderate certainty evidence (MCE); yellow, low certainty evidence (LCE); and red, very low certainty evidence (VLCE).

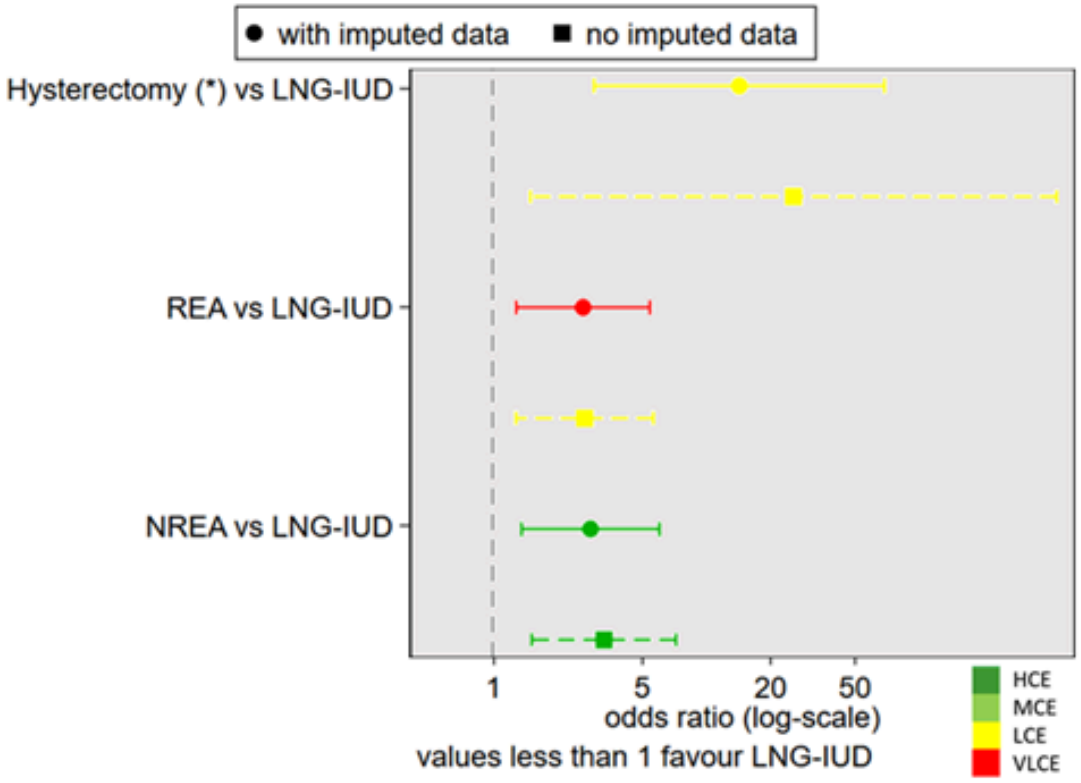
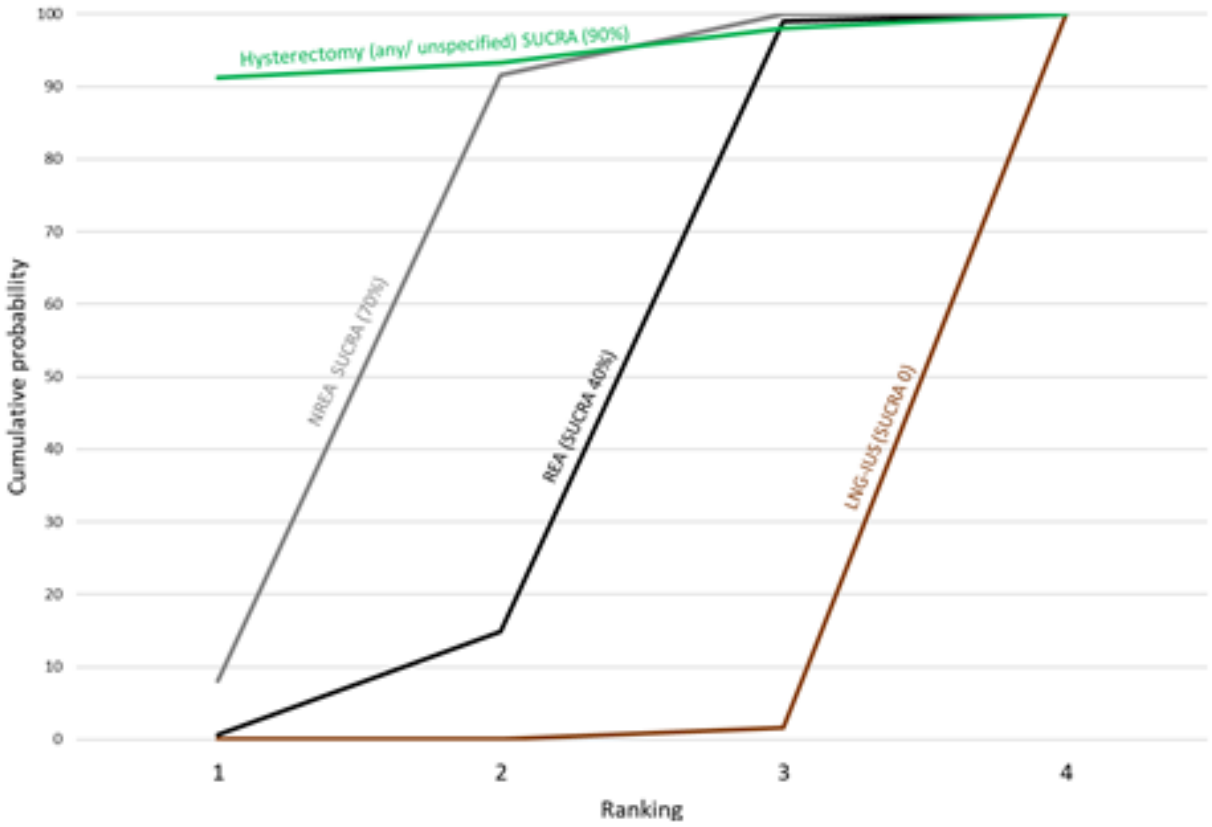


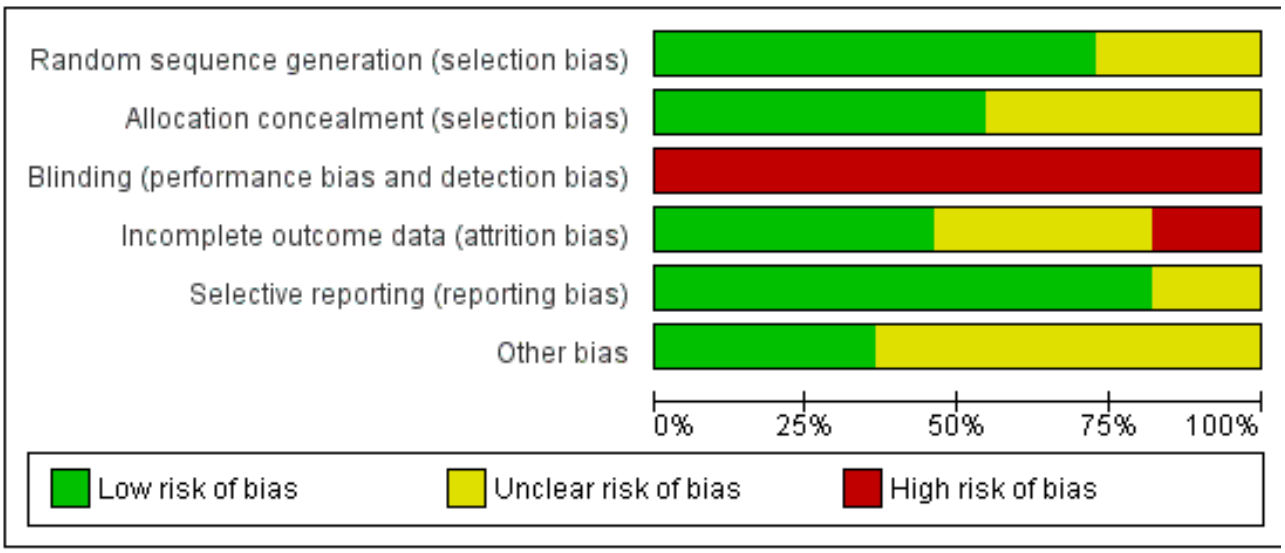
Figure 25. Cumulative rankogram comparing each treatment for bleeding (PBAC) improvement for second-line treatments. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface under the curve is a cumulative ranking line (SUCRA); the larger the SUCRA the higher its rank among all available treatments.



- The best second-line treatment without imputed data regarding bleeding improvement was hysterectomy (SUCRA 90%, mean rank 1.2, OR 25.71, 95% CI 1.50 to 439.96; low certainty evidence).
- Second, NREA (SUCRA 70%, mean rank 2.0, OR 3.32, 95% CI 1.53 to 7.23; moderate certainty evidence).
- Third, REA (SUCRA 40%, mean rank 2.8, OR 2.70, 95% CI 1.29 to 5.66; low certainty evidence).
- Worst, LNG-IUS (SUCRA 0%, mean rank 4, reference comparator).

Figure 26 summarises the risk of bias of each trial contributing data to the NMA. All trials were at either low or unknown risk of selection bias (random sequence generation and allocation concealment), selective reporting and other bias (such as baseline characteristics), but all trials were at high risk of performance and detection bias (blinding), as blinding is impossible between some of the interventions. We are uncertain whether the outcome is likely to be influenced by the lack of blinding. The risk of attrition bias (incomplete outcome data) was low or unclear in 80% of trials.

Figure 26. Risk of bias of studies included on the network for for bleeding (PBAC) improvement for second-line treatments.

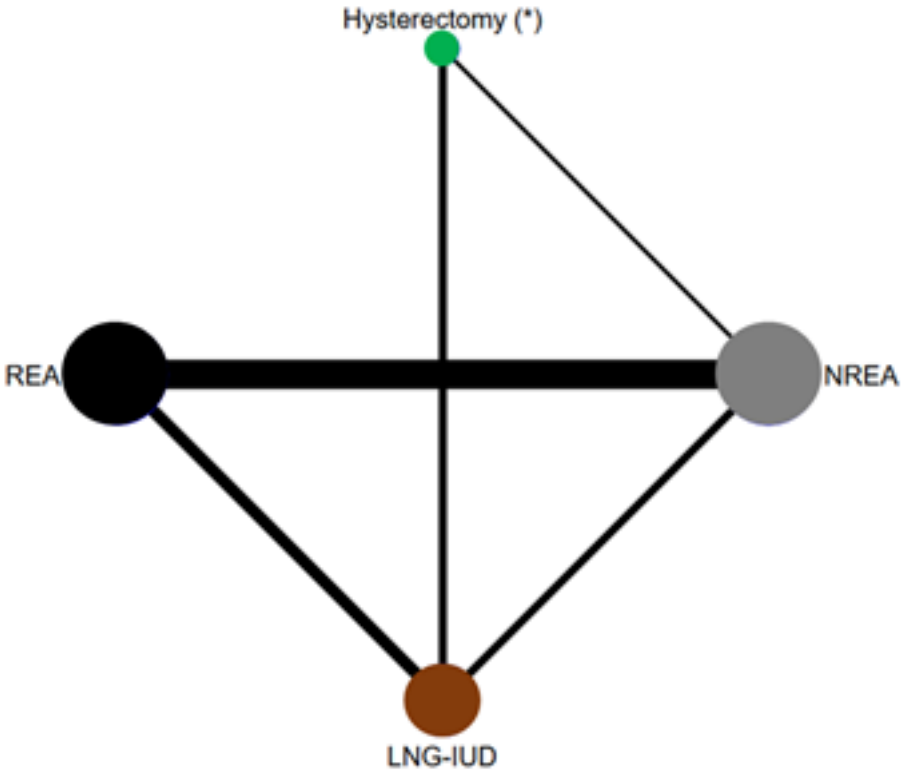


Bleeding improvement with imputed data

We imputed data from the mean PBAC value at one year, which a very limited number of studies reported (see Appendix 8 for imputation details) and combined it with the proportion with PBAC under 75 points or acceptable bleeding improvement. We obtained data from 15 studies comparing four interventions: LNG-IUS, REA, NREA and hysterectomy. See Table 14 for the summary of findings table for this outcome.

The network is connected: Figure 27 presents the NMA diagram for PBAC improvement with imputed data.

Figure 27. Network for bleeding (PBAC) improvement for second-line treatmentswith imputed data (15 studies, five treatments). The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Multiarm trials contribute to more than one comparison.

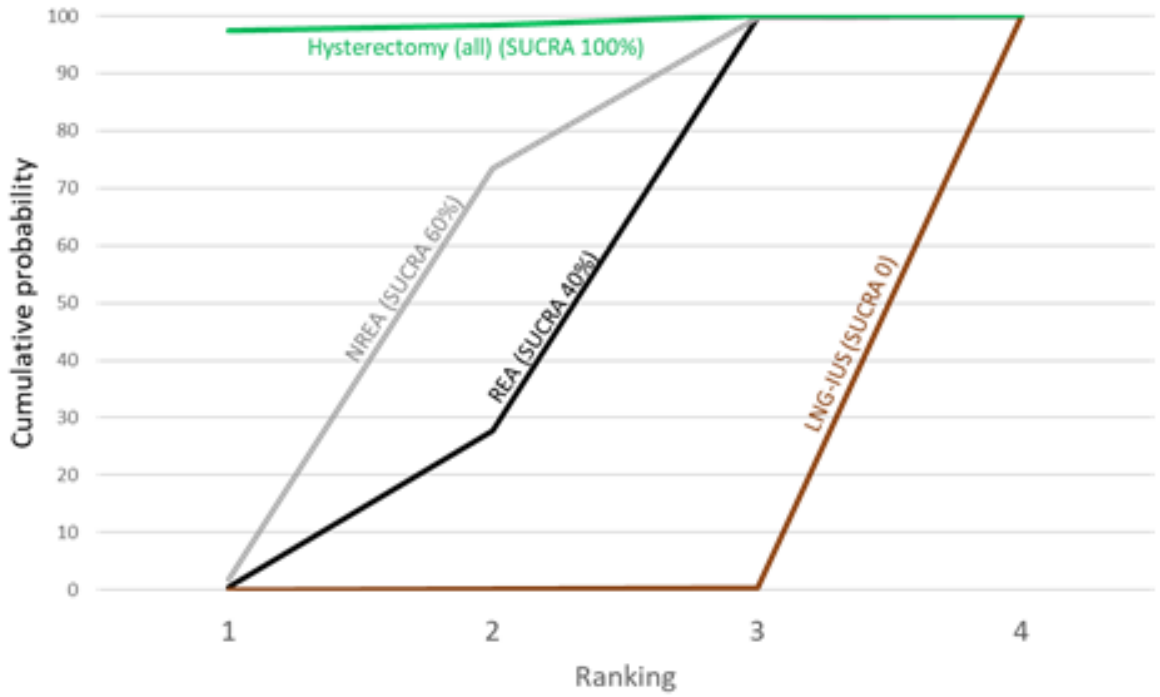


There is no evidence of inconsistency using the node-split or inconsistency models in comparisons (P value for inconsistency model is 0.26). We used the fixed-effect model. See consistency details in Appendix 9.

See Figure 24 for the forest plot (combined with and without imputed data).

Figure 28 shows the cumulative probabilities for each treatment at each possible rank for improving the PBAC.

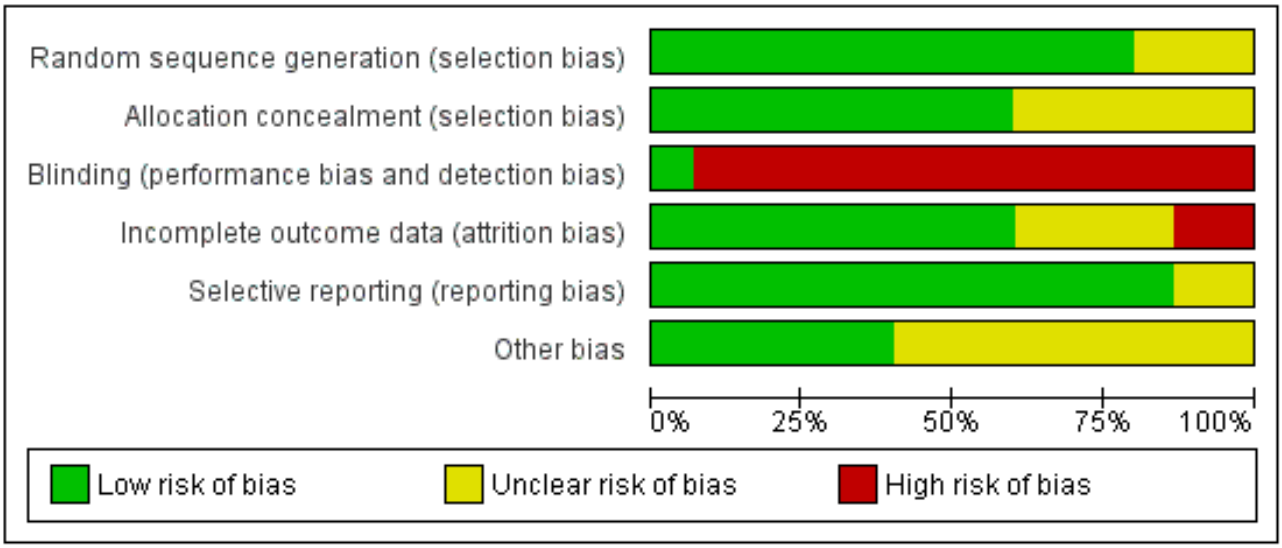
Figure 28. Cumulative rankogram comparing each treatment for bleeding (PBAC) improvement with imputed data for second-line treatments. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface under the curve is a cumulative ranking line (SUCRA); the larger the SUCRA the higher its rank among all available treatments.



- The best second-line treatment for the bleeding improvement (with imputed data) was hysterectomy (SUCRA 100%, mean rank 1.0, OR 14.31, 95% CI 2.99 to 68.56; low certainty evidence).
- Second, NREA (SUCRA 60%, mean rank 2.2, OR 2.87, 95% CI 1.29 to 6.05; moderate certainty evidence).
- Third, REA (SUCRA 40%, mean rank 2.7, OR 2.65, 95% CI 1.29 to 5.45; very low certainty evidence).
- Worst, LNG-IUS (SUCRA 0%, mean rank 4, reference comparator).

Figure 29 shows the risk of bias of each trial contributing with data to the NMA. The risk of selection bias (random sequence generation and allocation concealment), selective reporting and other bias (such as baseline characteristics) was either low or unknown in all trials, while performance and detection bias (blinding) were at high risk in 90%, because although blinding may be feasible between different endometrial ablation techniques, it is almost impossible between the other interventions. We are uncertain whether the outcome is likely to be influenced by the lack of blinding. The risk of attrition bias (incomplete outcome data) was low or unclear in 80% of trials.

Figure 29. Risk of bias of studies included on the network for for bleeding (PBAC) improvement for second-line treatmentswith imputed data.

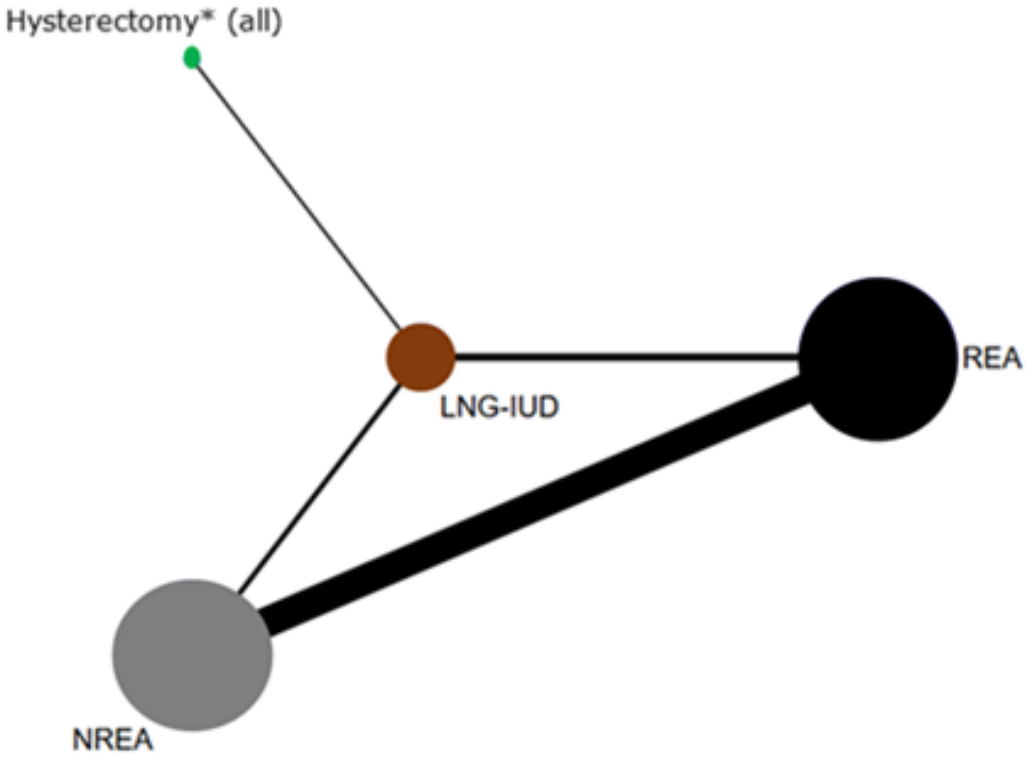


Amenorrhoea

Eighteen studies reported the rate of amenorrhoea up to one year, comparing four treatments: REA, NREA, LNG-IUS and hysterectomy. See Table 15 for the summary of findings table for this outcome.

The network is connected: Figure 30 presents the NMA diagram for amenorrhoea.

Figure 30. Network for amenorrhoea at one year for second-line treatments (18 studies, 4 treatments). The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison.Multiarm trials contribute to more than one comparison.



There is no evidence of inconsistency using the node-split or inconsistency models (P value for inconsistency model 0.24). We used the fixed-effect model. See consistency details in Appendix 10.

See Figure 31 for the forest plot. Figure 32 shows the cumulative probabilities for each treatment at each possible rank for achieving amenorrhoea.

Figure 31. Forest plot amenorrhoea for second-line treatments. All evidence has very low certainty. All evidence has very low certainty.

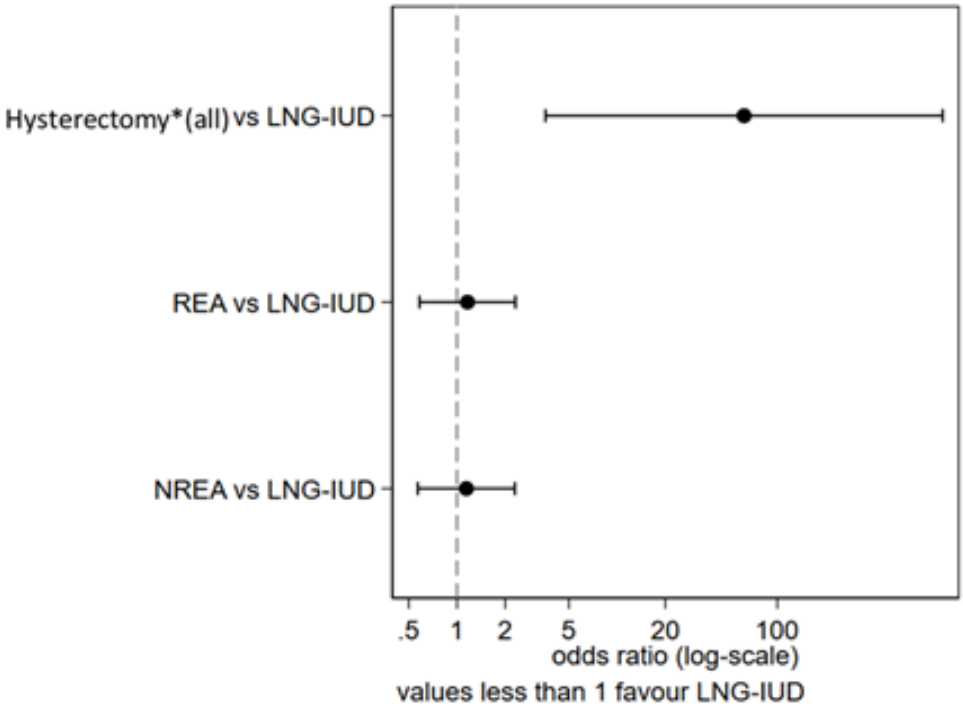
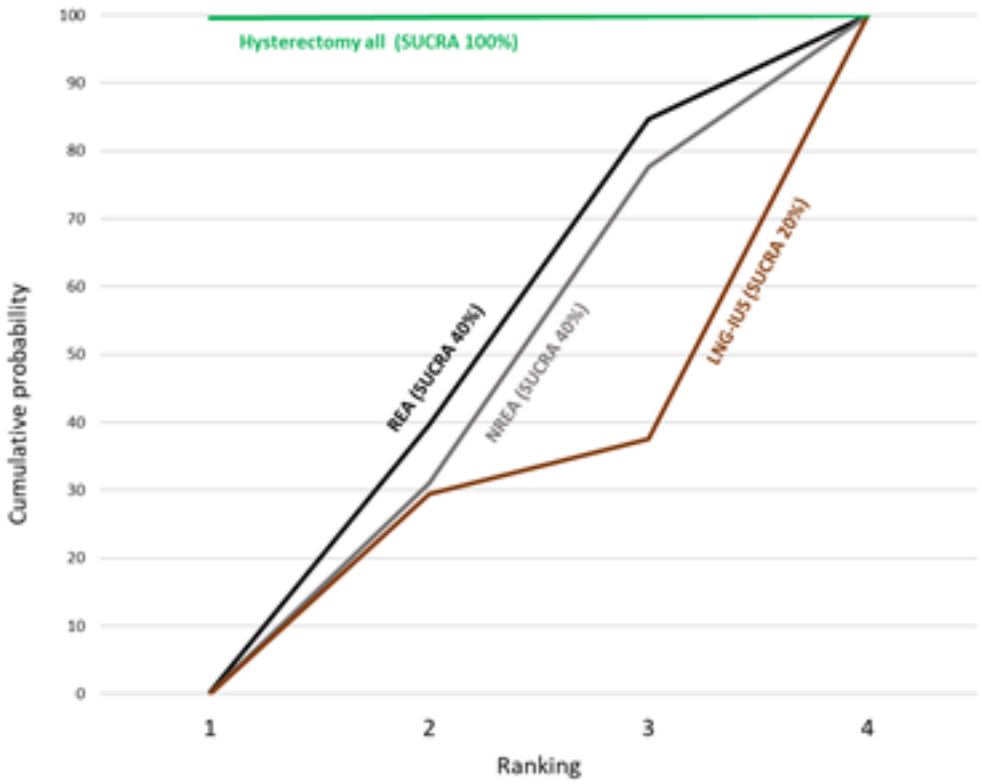


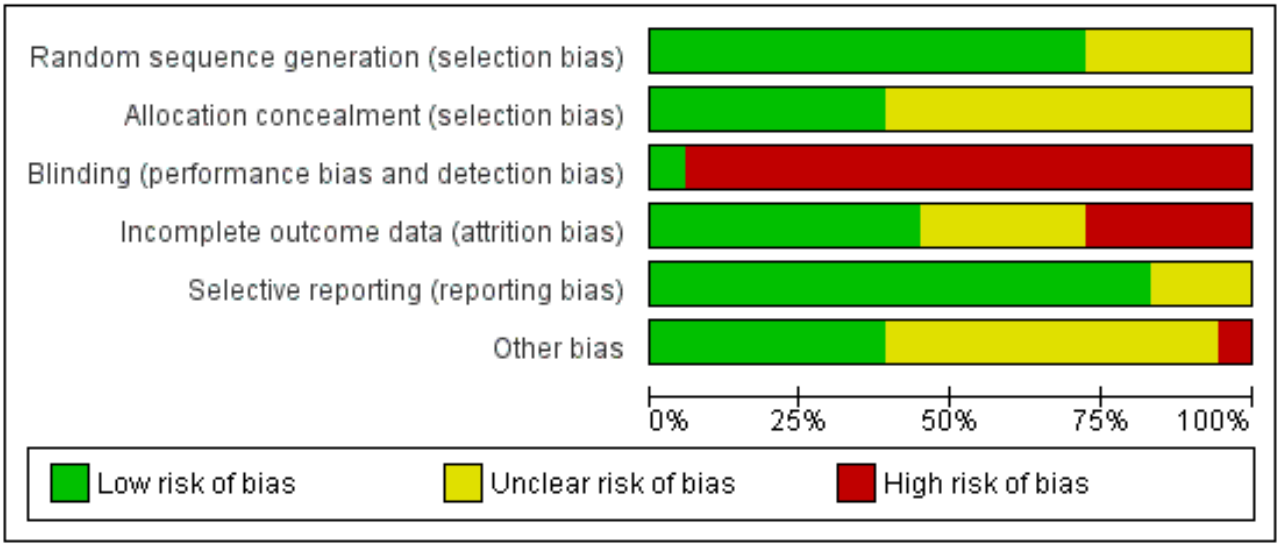
Figure 32. Cumulative rankogram comparing each treatment for amenorrhoea at one year follow-up for second-line treatments. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface under the curve is a cumulative ranking line (SUCRA); the larger the SUCRA the higher its rank among all available treatments.



- The best second-line treatment for the bleeding improvement was hysterectomy (SUCRA 100%, mean rank 1.0, OR 62.11, 95% CI 3.57 to 1079.05; very low certainty evidence).
- Second, REA (SUCRA 40%, mean rank 2.8, OR 1.16, 95% CI 0.58 to 2.31; very low certainty evidence).
- Third, NREA (SUCRA 40%, mean rank 2.9 respectively, OR 1.14, 95% CI 0.57 to 2.29; very low certainty evidence).
- Worst, LNG-IUS (SUCRA 20%, mean rank 3.3, reference comparator).

Figure 33 summarises the risk of bias of each trial contributing with data to the NMA. All trials were at either low or unknown risk of selection bias (random sequence generation and allocation concealment) and selective reporting, while 90% were at high risk of performance and detection bias (blinding), because even though blinding is feasible between different endometrial ablation and resection procedures, it is very unlikely with LNG-IUS insertion or open surgery. The outcome is likely to be influenced by the lack of blinding. The risk of attrition bias (incomplete outcome data) was low or unclear in 80% of trials, and over 90% of trials were at unclear or low risk of other bias (such as baseline characteristics).

Figure 33. Risk of bias of studies contributing with direct evidence for the network for amenorrhoea for second-line treatments.

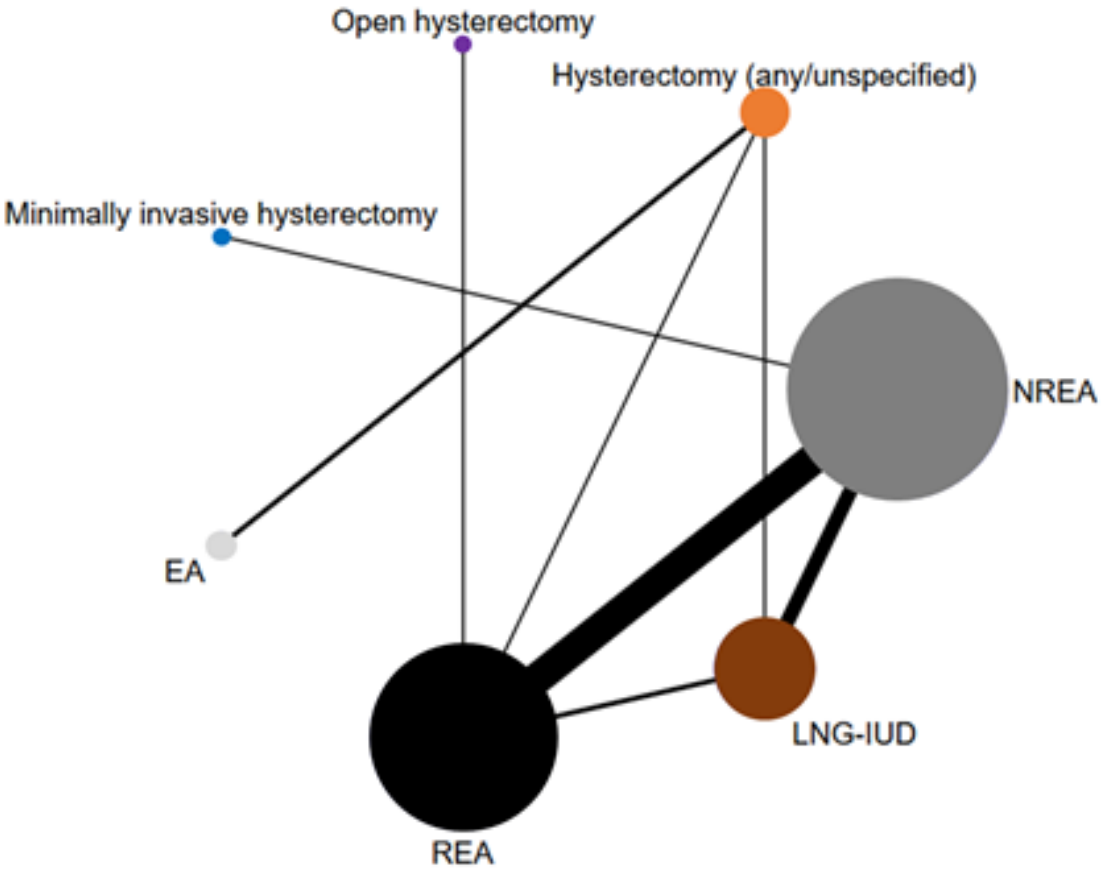


2. Satisfaction

Twenty-seven studies reported the rate of satisfaction with treatment at up to one year follow-up, comparing seven treatments: REA, NREA, EA (unspecified), LNG-IUS, hysterectomy (any/unspecified), minimally invasive hysterectomy and open hysterectomy. See Table 16 for the summary of findings table for this outcome.

The network is connected: Figure 34 presents the NMA diagram for satisfaction.

Figure 34. Network for satisfaction for second-line treatments (27 studies, seven treatments). The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Multiarm trials contribute to more than one comparison.



There are two loops in the network. There is no evidence of inconsistency using the node-split or inconsistency models (P value for inconsistency model 0.25). We used the fixed-effect model. See consistency details in Appendix 11.

See Figure 35 for the forest plot. Figure 36 shows the cumulative probabilities for each treatment at each possible rank for achieving satisfaction.

Figure 35. Forest plot for satisfaction. Second-line treatments. Colours of the lines are according to the certainty of the evidence: dark green, high certainty evidence (HCE); light green, moderate certainty evidence (MCE); yellow, low certainty evidence (LCE); and red, very low certainty evidence (VLCE).

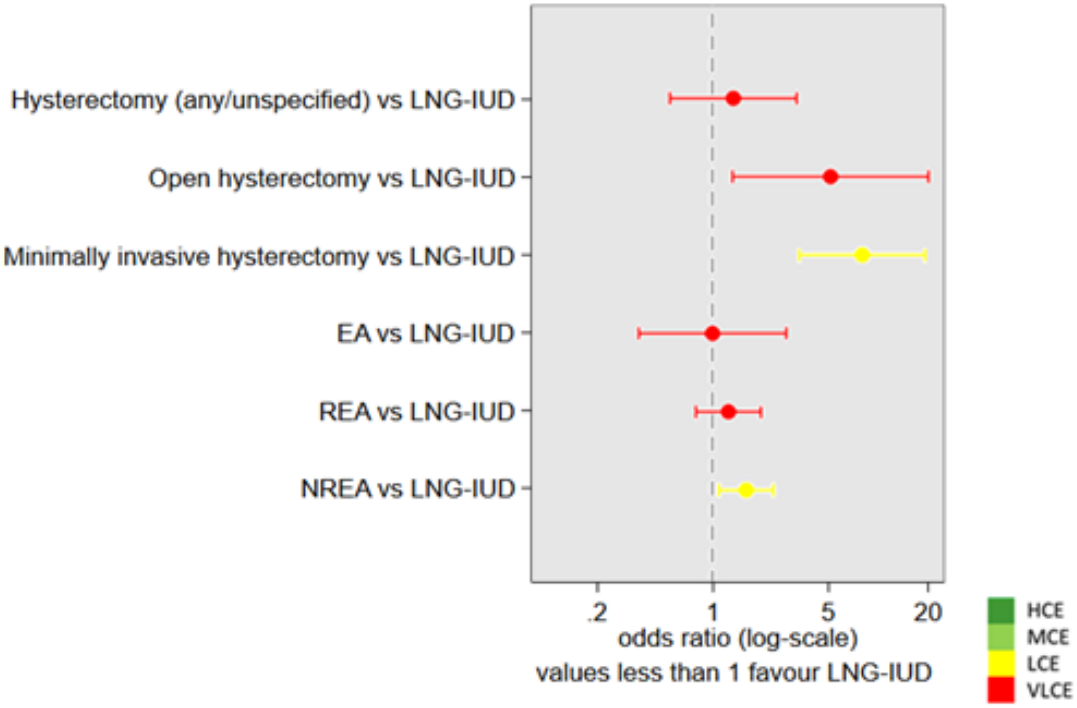
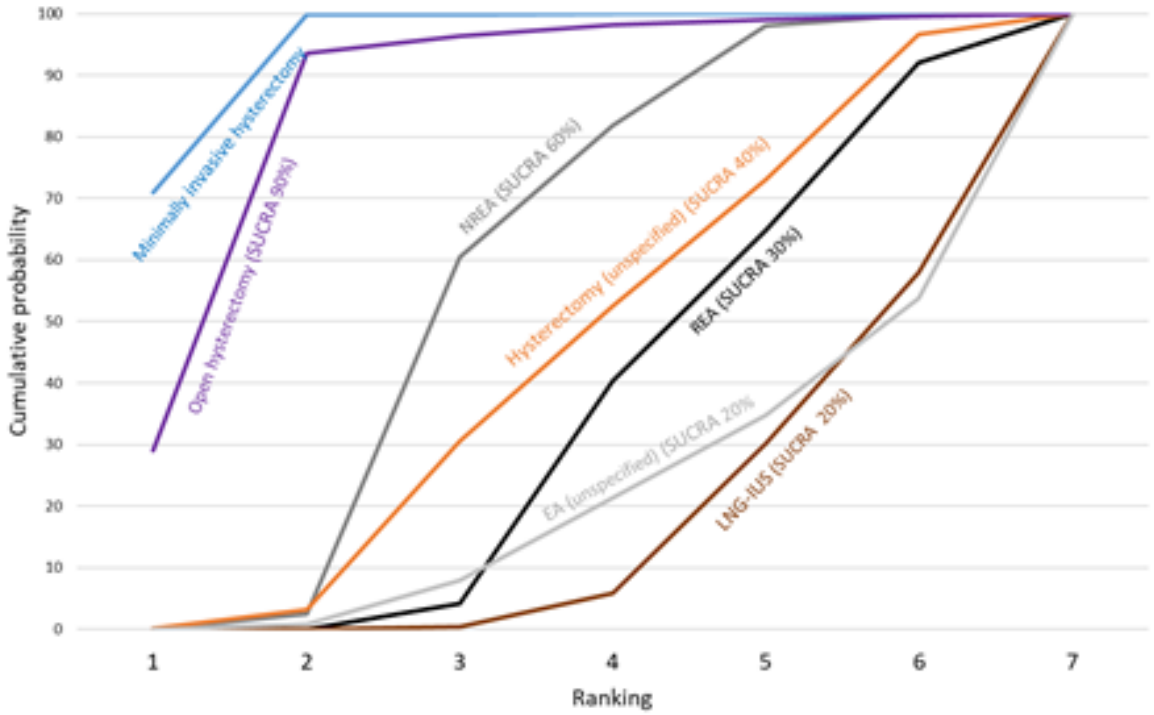


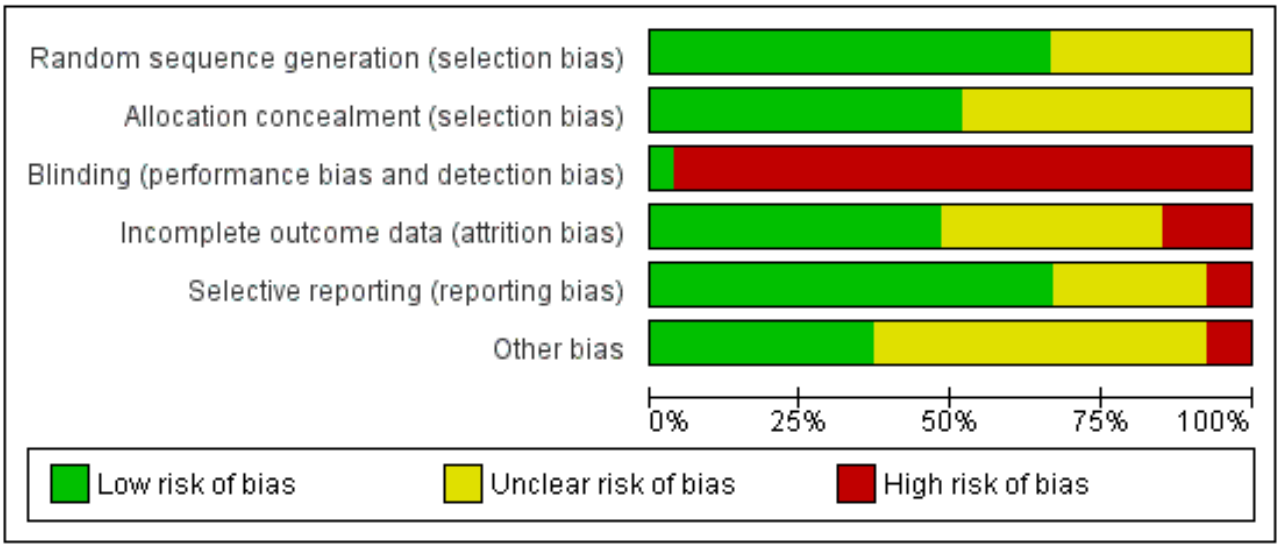
Figure 36. Cumulative rankogram comparing each treatment for satisfaction at one year follow-up for second-line treatments. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface under the curve is a cumulative ranking line (SUCRA); the larger the SUCRA the higher its rank among all available treatments.



- The best treatment in terms of satisfaction was minimally invasive hysterectomy (SUCRA 100%, mean rank 1.3, OR 7.96, 95% CI 3.33 to 19.03; low certainty evidence).
- Second, open hysterectomy (SUCRA 90%, mean rank 1.8, OR 5.13, 95% CI 1.32 to 19.92; very low certainty evidence).
- Third, NREA (SUCRA 60%, mean rank 3.6, OR 1.59, 95% CI 1.09 to 2.33; low certainty evidence).
- Fourth, hysterectomy (unspecified route) (SUCRA 40%, mean rank 4.4, OR 1.34, 95% CI 0.56 to 3.21; very low certainty evidence).
- Fifth, REA (SUCRA 30%, mean rank 5.0, OR 1.25, 95% CI 0.80 to 1.96; very low certainty evidence).
- Sixth, unspecified EA (SUCRA 20%, mean rank 5.8, OR 1.00, 95% CI 0.36 to 2.78; very low certainty evidence).
- Worst, LNG-IUS (SUCRA 20%, mean rank 6.1, reference comparator).

Figure 37 summarises the risk of bias of each trial contributing data to the NMA. All trials were at either low or unknown risk of selection bias (random sequence generation and allocation concealment), but 90% were at high risk of performance and detection bias (blinding), probably because blinding is feasible between different endometrial ablation and resection procedures, but it is difficult with LNG-IUS insertions and hysterectomies. The lack of blinding is likely to influence the outcome. Less than 20% of trials were at high risk for attrition (incomplete outcome data), reporting and other bias.

Figure 37. Risk of bias of studies included on the network for satisfaction for second-line treatments.



Secondary outcomes

1. Quality of life

There was substantial disagreement between the direct and indirect evidence comparing NREA to minimally invasive hysterectomy ((D) Sesti 2011). This caused substantial inconsistency in the network (node-split model P < 0.001 and inconsistency model P < 0.001). In addition, inspection of the study estimates showed that the two studies comparing NREA and LNG-IUS provide substantially different estimates of this relative treatment effect ((D) Talis 2006; (D) Tam 2006). We therefore decided not to formally combine these results in an NMA and do not present results. Instead, we present the results from pairwise comparisons. Seven trials reported quality of life up to two years using the SF-36 and one, the Menorrhagia Multiatribute Scale (MMAS). The MMAS was reported dichotomously as the proportion with MMAS = 1, which is the best possible result. See Table 17 for the summary of findings for this outcome.

Data showed that there may be little to no difference on the following comparisons using the SF-36.

- EA (unspecified) versus hysterectomy (unspecified route): MD −1.90 points, 95% CI −8.67 to 4.87; 1 study, 204 women; low certainty evidence).
- NREA versus LNG-IUS: MD 2.9 points, 95% CI −3.10 to 9.02; I^2 =81%; 2 studies, 98 women; low certainty evidence).

The comparison reported evidence of difference using the SF-36.

- Evidence favours minimally invasive hysterectomy compared to NREA (MD −10.90 points, 95% CI −15.81 to −5.99; 1 study, 68 women; low certainty evidence).

The comparisons reported difference using the MMAS.

- Women having minimally invasive hysterectomy are probably more likely to have a better quality of life measured with MMAS compared to the NREA (RR 0.82, 95% CI 0.70 to 0.95; 1 study, 616 participants; moderate certainty evidence).

The evidence is very uncertain about the following comparisons.

- REA versus minimally invasive hysterectomy (MD −9.90 points, 95% CI −19.89 to 0.09; 1 study, 67 women; very low certainty evidence).
- REA versus open hysterectomy (MD −5.30 points, 95% CI −11.90 to 1.30; 1 study, 155 women; very low certainty evidence).
- Minimally invasive hysterectomy versus LNG-IUS (MD −1.50 points, 95% CI −4.28 to 1.28; 1 study, 72 women; very low certainty evidence)
- LNG-IUS versus hysterectomy (unspecified, or at surgeon's discretion) (MD 2.20 points, 95% CI −2.93 to 7.33; 1 study, 221 women; very low certainty evidence).

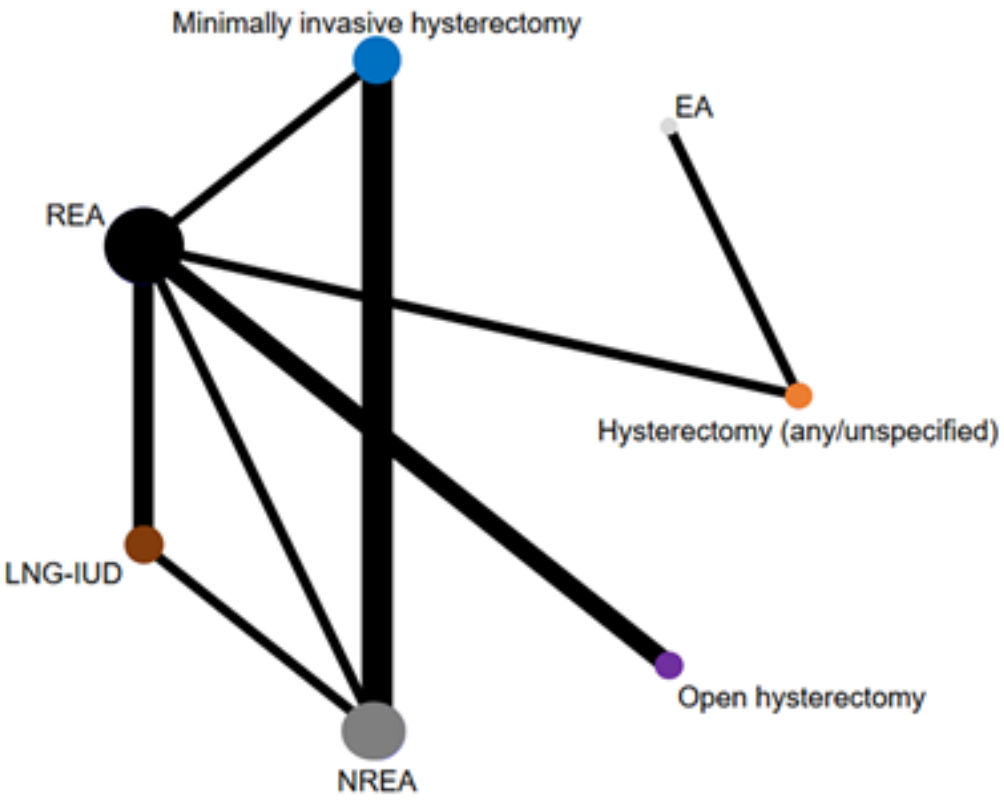
2. Adverse events

Trials mostly reported individual adverse events, and we were unable to group them due to the risk of double counting.

Twelve studies comparing six treatments (LNG-IUS, REA, NREA, minimally invasive hysterectomy, open hysterectomy and hysterectomy (any/unspecified)) reported 'any adverse event'. The severity of the outcome varied among studies, which reported infection, bladder injury, haematoma, uterine perforation, blood transfusion, pelvic pain, vaginal discharge, abdominal pain, breast tenderness, headache, acne, mood changes, genital ulceration, decreased libido, hair loss, acne, anxiety-depression, hypertension and leg pain. See Table 18 for the summary of findings table for this outcome.

The network is connected; Figure 38 presents the NMA diagram for any adverse events.

Figure 38. Network for any adverse event for second-line treatments. The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Multiarm trials contribute to more than one comparison.



There is no evidence of inconsistency using the node-split or inconsistency models (P = 0.43). See consistency details in Appendix 12. We used the fixed-effect model.

See the forest plot in Figure 39.

Figure 39. Forest plot for any adverse events for second-line treatments

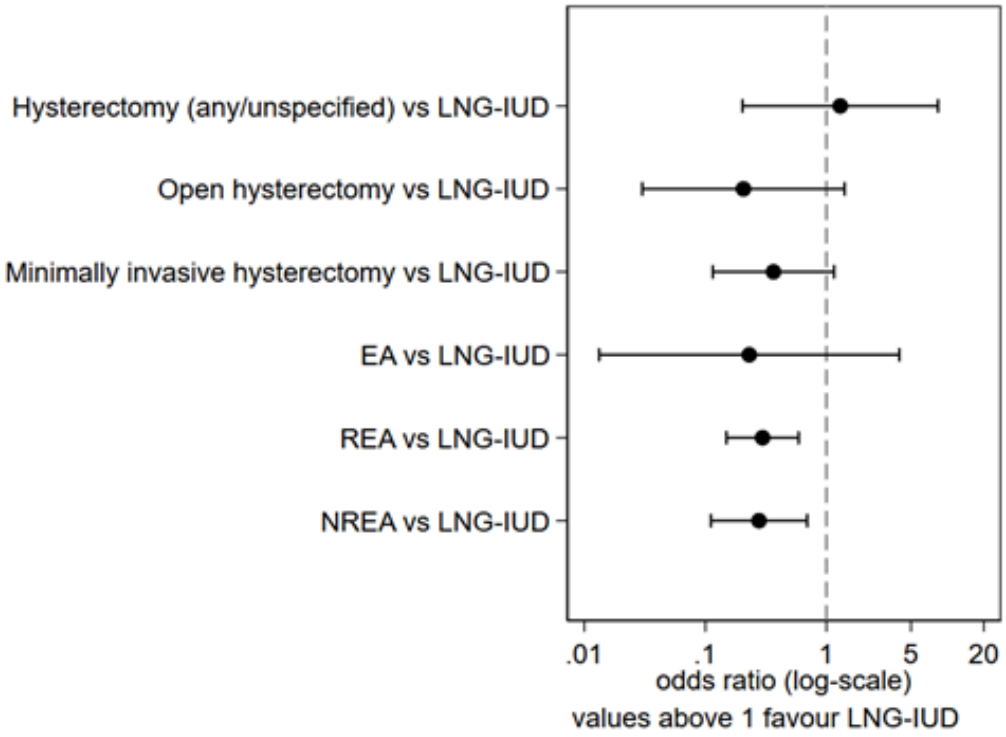
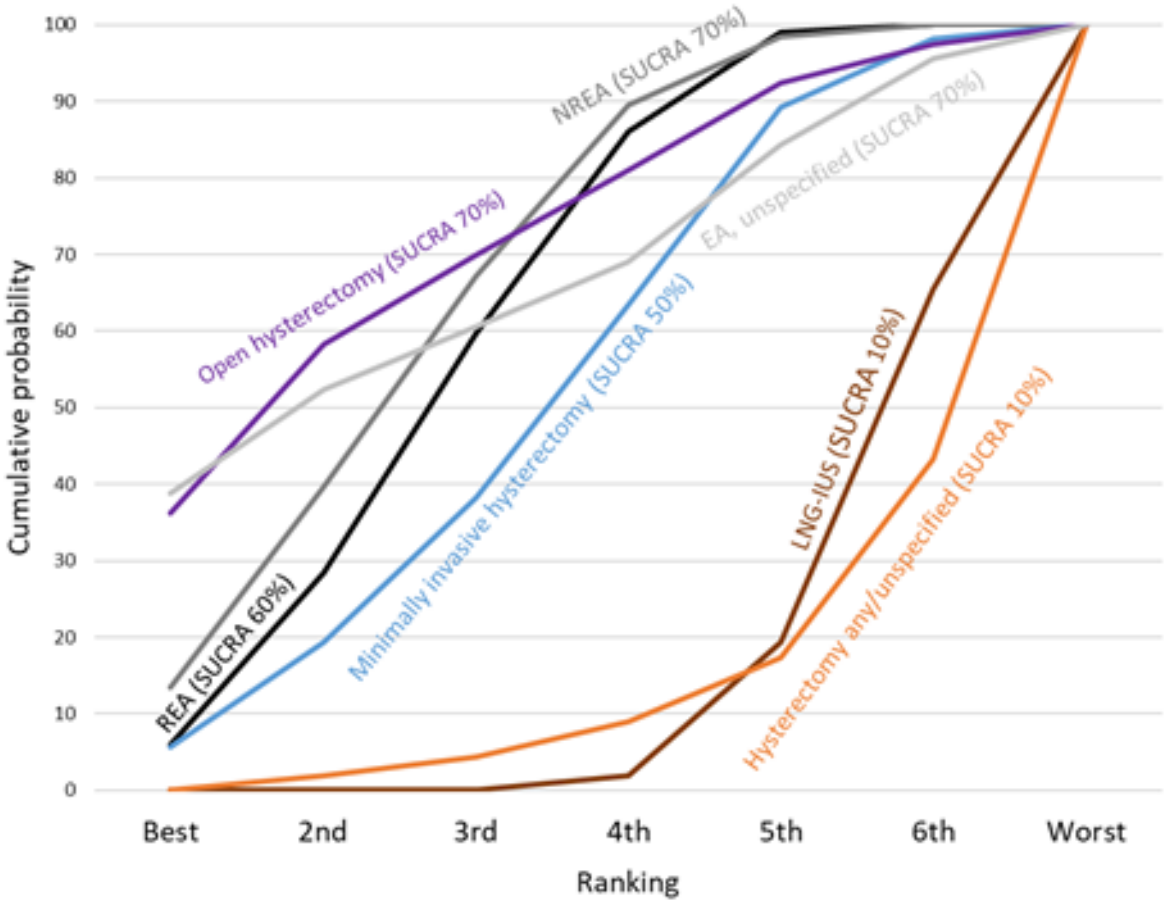


Figure 40 shows the cumulative probabilities for each treatment at each possible rank for having any adverse events of any degree (having less).

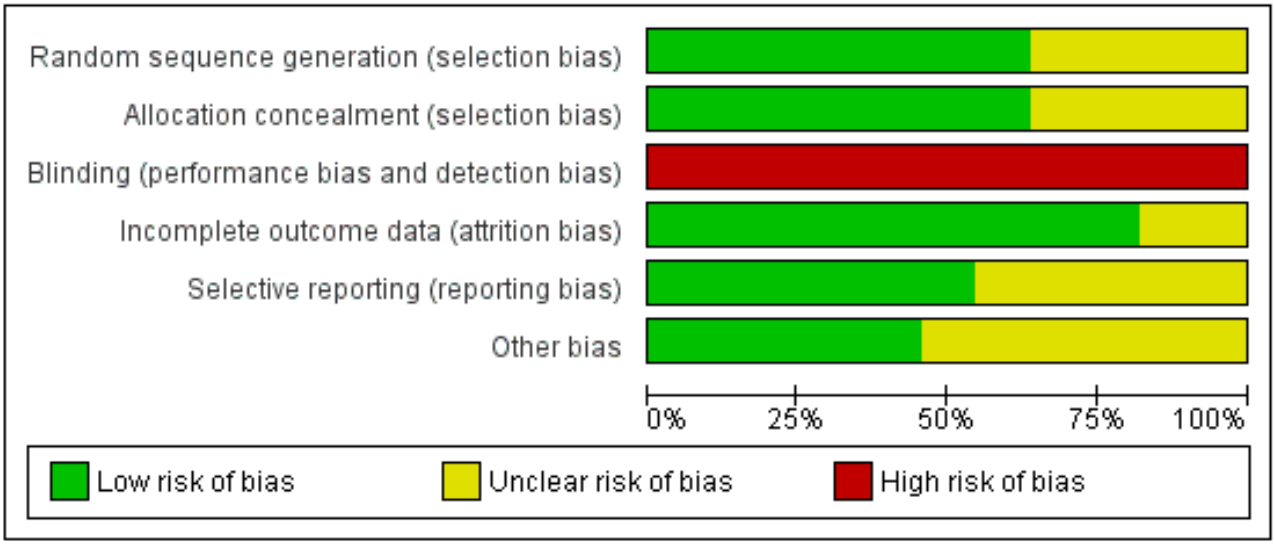
Figure 40. Cumulative rankogram comparing each treatment for any adverse events for second-line treatments. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface under the curve is a cumulative ranking line (SUCRA); the larger the SUCRA the higher its rank among all available treatments.



- The best treatment in terms of adverse events (that is, the least likely to produce any), was open hysterectomy (SUCRA 70%, mean rank 2.6, OR 0.21, 95% CI 0.30 to 1.41; very low certainty evidence).
- Second, NREA (SUCRA 70%, mean rank 2.9, OR 0.28, 95% CI 0.11 to 0.69; very low certainty evidence).
- Third, EA (any or unspecified) (SUCRA 70%, mean rank 3.0, OR 0.23, 95% CI 0.01 to 4.00; very low certainty evidence).
- Fourth, REA (SUCRA 60%, mean rank 3.2, OR 0.29, 95% CI 0.15 to 0.59; very low certainty evidence).
- Fifth, minimally invasive hysterectomy (SUCRA 50%, mean rank 3.9, OR 0.36, 95% CI 0.11 to 1.16; very low certainty evidence).
- Sixth, LNG-IUS (SUCRA 10%, mean rank 6.1, reference comparator).
- Worst, hysterectomy (unspecified or surgeon's choice of route of hysterectomy) (SUCRA 10%, mean rank 6.2, OR 1.30, 95% CI 0.20 to 8.37; very low certainty evidence).

Figure 41 summarises the risk of bias of each trial contributing data to the NMA. All trials were at either low or unknown risk of selection bias (random sequence generation and allocation concealment), attrition, reporting and other bias, but they were all at high risk of performance and detection bias (blinding), as blinding is feasible only between different endometrial ablation and resection procedures, less likely with LNG-IUS compared to EAs procedures, and impossible with hysterectomies. The outcome is likely to be influenced by the lack of blinding.

Figure 41. Risk of bias of studies contributing with direct evidence for any adverse events for second-line treatments.



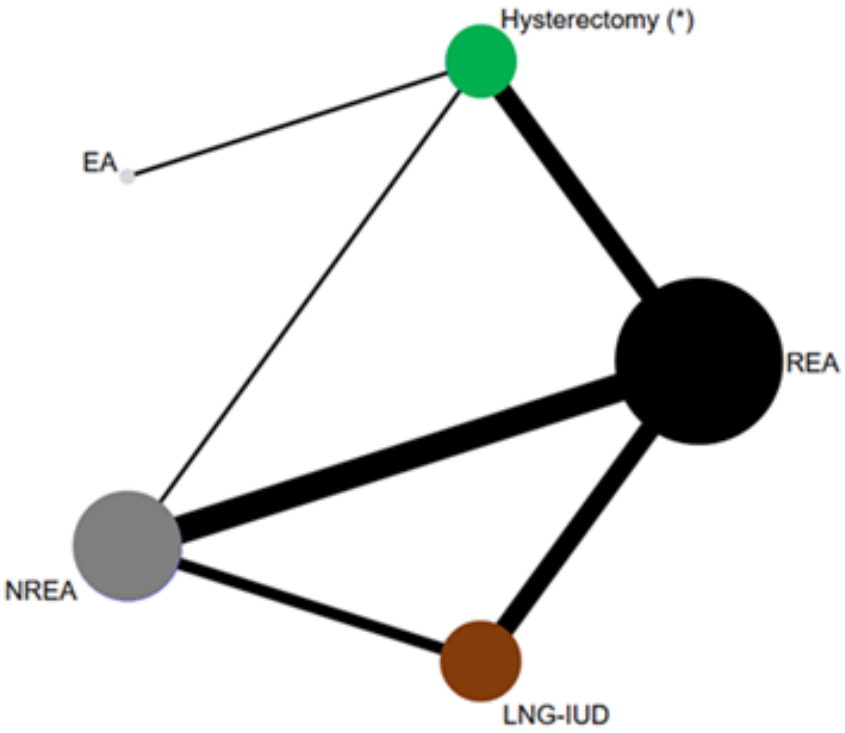
3. Requirement of further surgery

For this outcome, we grouped all hysterectomy routes as one intervention (hysterectomy).

The requirement of further surgery for HMB was reported in 22 trials, comparing four treatments: REA, NREA, EA (unspecified), LNG-IUS and hysterectomy. See Table 19 for the summary of findings table for this outcome.

The network is connected: Figure 42 presents the NMA diagram for requirement of further surgery for HMB treatment. There is no evidence of inconsistency using the node-split or inconsistency models (P value for inconsistency model 0.73). See consistency details in Appendix 13. We used the fixed-effect model.

Figure 42. Network for requirement of further surgery (22 studies, seven treatments) for second-line treatments. The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Multiarm trials contribute to more than one comparison.



See the forest plot in Figure 43. Figure 44 presents the cumulative probabilities for each treatment at each possible rank for requirement of further surgery (requiring less).

Figure 43. Forest plot for the requirement of further surgery for the treatment of heavy menstrual bleeding. Second-line treatments. Colours of the lines are according to the certainty of the evidence: dark green, high certainty evidence (HCE); light green, moderate certainty evidence (MCE); yellow, low certainty evidence (LCE); and red, very low certainty evidence (VLCE).

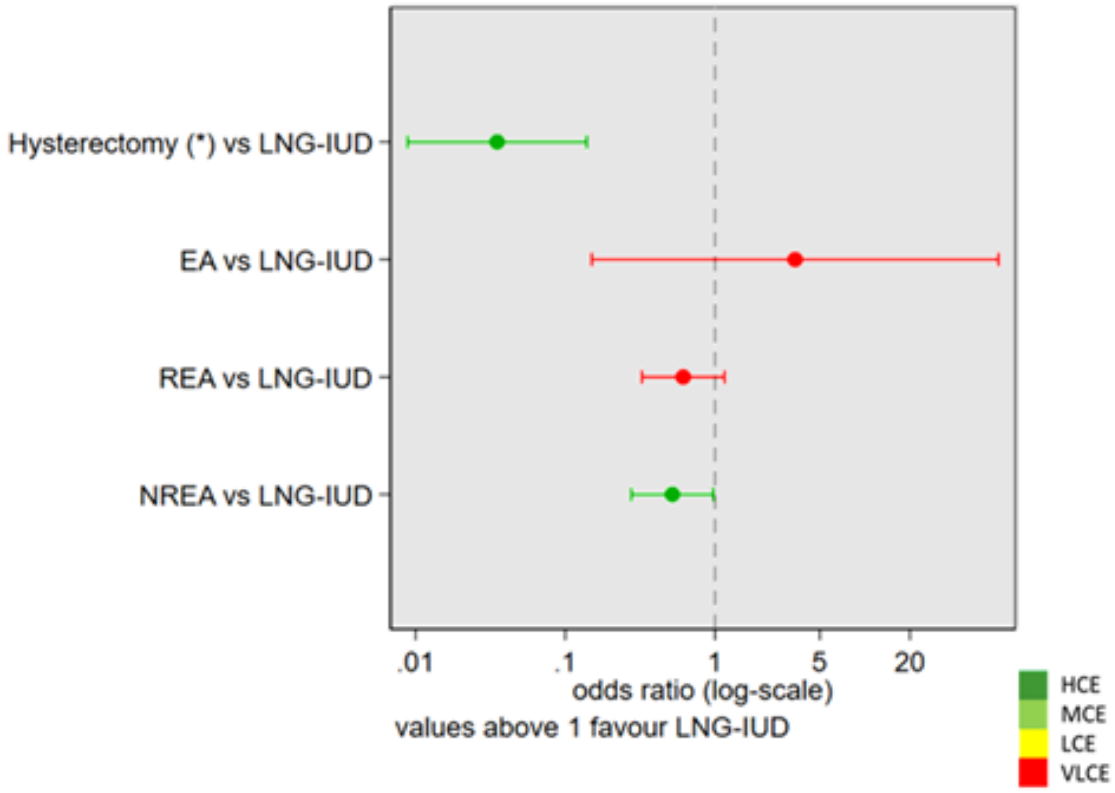
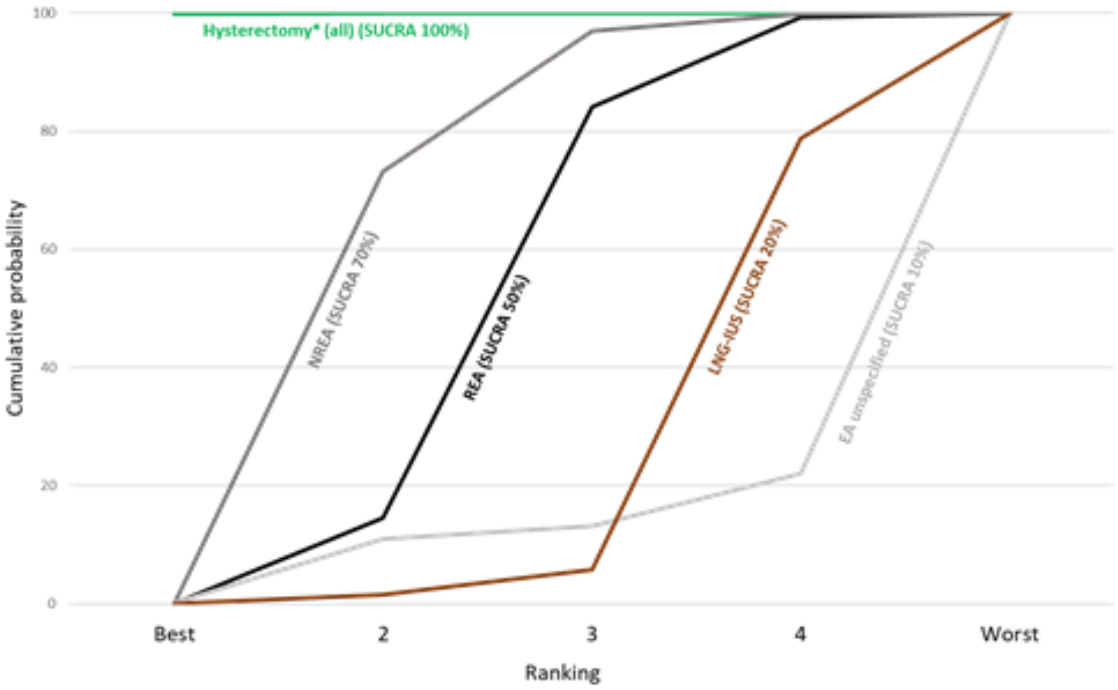


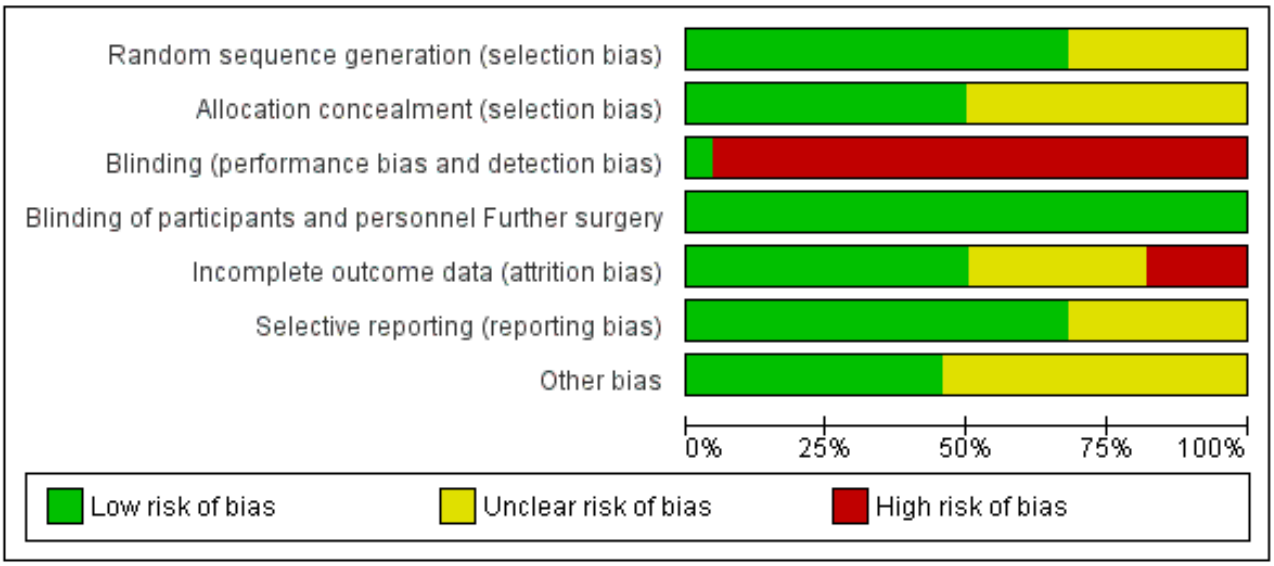
Figure 44. Cumulative rankogram comparing each treatment for requirement of further surgery for HMBat one year follow-up for second-line treatments. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface under the curve is a cumulative ranking line (SUCRA); the larger the SUCRA the higher its rank among all available treatments.



- The best treatment in terms of the requirement of further surgery for HMB is hysterectomy (SUCRA 100%, mean rank 1.0, OR 0.03, 95% CI 0.01 to 0.13; moderate certainty evidence).
- Second, NREA (SUCRA 70%, mean rank 2.3, OR 0.52, 95% CI 0.28 to 0.97; moderate certainty evidence).
- Third, REA (SUCRA 50%, mean rank 3, OR 0.61, 95% CI 0.32 to 1.15; very low certainty evidence).
- Fourth, LNG-IUS (SUCRA 20%, mean rank 4.1, reference comparator).
- Worst, EA (any/unspecified) (SUCRA 10%, mean rank 4.5, OR 3.42, 95% CI 0.14 to 78.19; very low certainty evidence).

Figure 45 summarises the risk of bias of trials contributing with data to the NMA. All trials were at either low or unknown risk of selection bias (random sequence generation and allocation concealment), reporting and other bias, but over 90% were at high risk of performance and detection bias (blinding), as blinding is feasible only between different endometrial ablation and resection procedures, less likely with LNG-IUS compared to EA procedures, and impossible with hysterectomies. Lack of blinding may be less likely to interfere with the requirement of further surgery compared to other outcomes.

Figure 45. Risk of bias of studies included on the network for requirement of further surgery for second-line treatments.



Subgroup analysis

Endometrial resection and ablation procedures (EA)

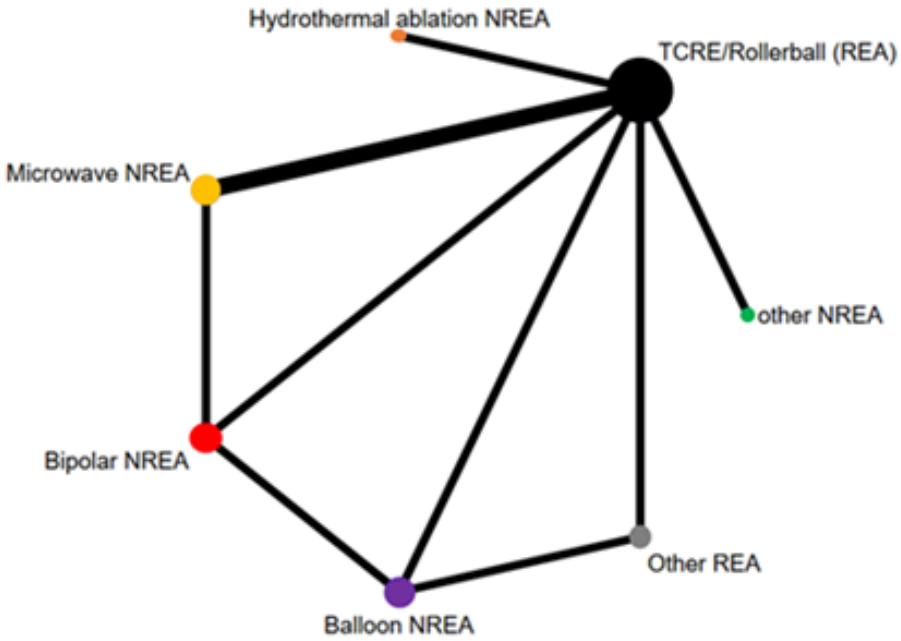
1. Menstrual blood loss reduction (subgroup EA)

Pictorial blood assessment chart (PBAC) improvement

Ten studies reported PBAC improvement, comparing seven EA procedures: TCRE with or without rollerball, other REA, microwave NREA, hydrothermal ablation NREA, bipolar NREA, balloon NREA and other NREA. See Table 20 for the summary of findings table for this outcome.

The network is connected. See Figure 46 for network diagram.

Figure 46. Subgroup analysis EA. Network, bleeding (PBAC) improvement at one year follow-up. The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Multiarm trials contribute to more than one comparison.



We used the fixed-effect model. There were only a few studies per comparison. There was evidence of inconsistency using the node-split model in two comparisons (TCRE/rollerball versus microwave NREA and microwave NREA versus bipolar NREA); and in the inconsistency model (P value for inconsistency 0.002). Results should be interpreted with caution due to inconsistency. See Appendix 14.

See forest plot in Figure 47.

Figure 47. Subgroup analysis EA. Forest plot bleeding (PBAC) improvement. Colours of the lines are according to the certainty of the evidence: dark green, high certainty evidence (HCE); light green, moderate certainty evidence (MCE); yellow, low certainty evidence (LCE); and red, very low certainty evidence (VLCE).

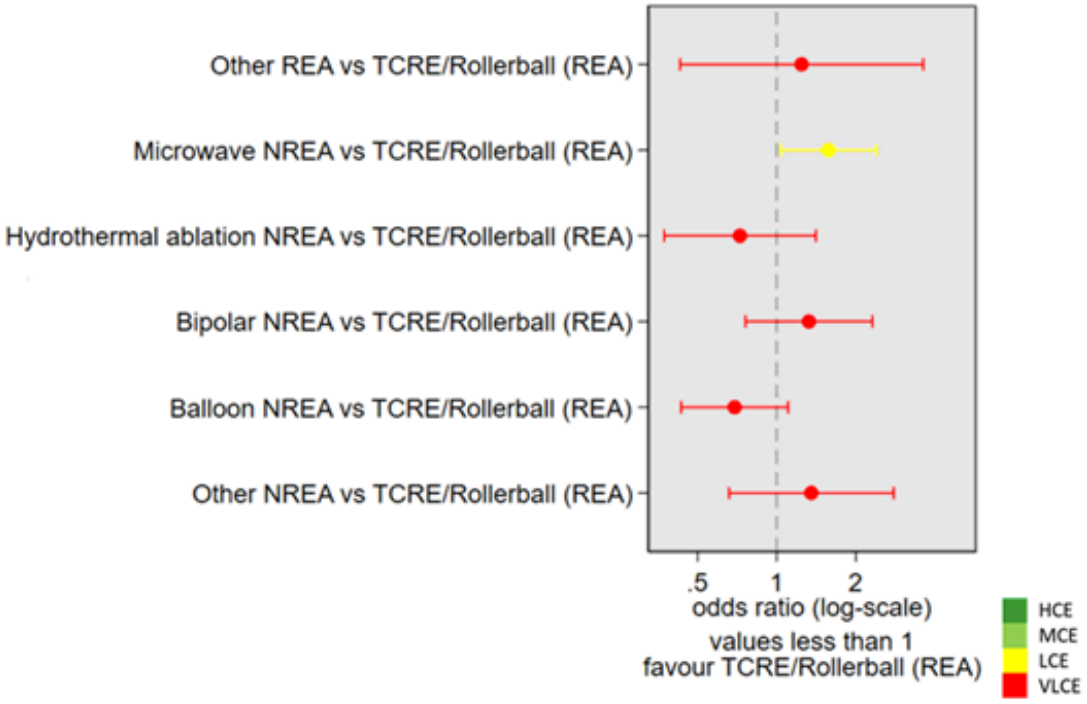
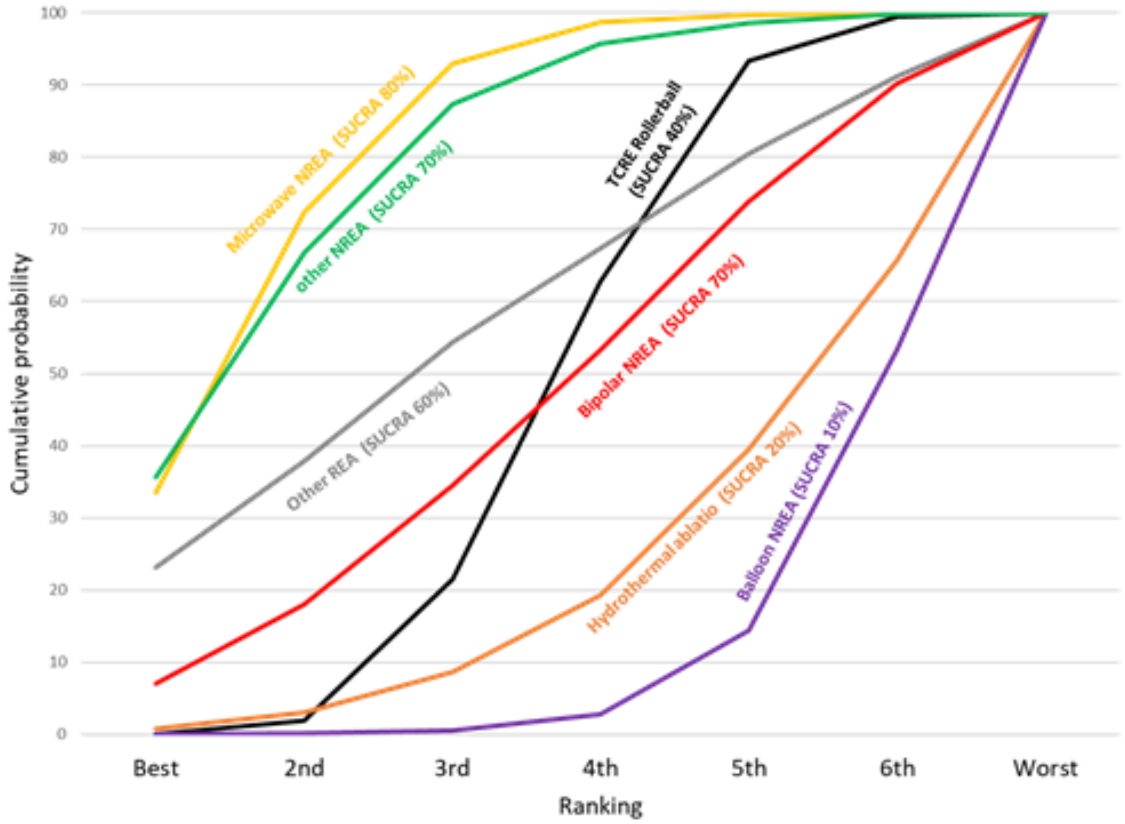


Figure 48 presents the cumulative probabilities for each treatment at each possible rank for bleeding (PBAC) improvement at one year follow-up.

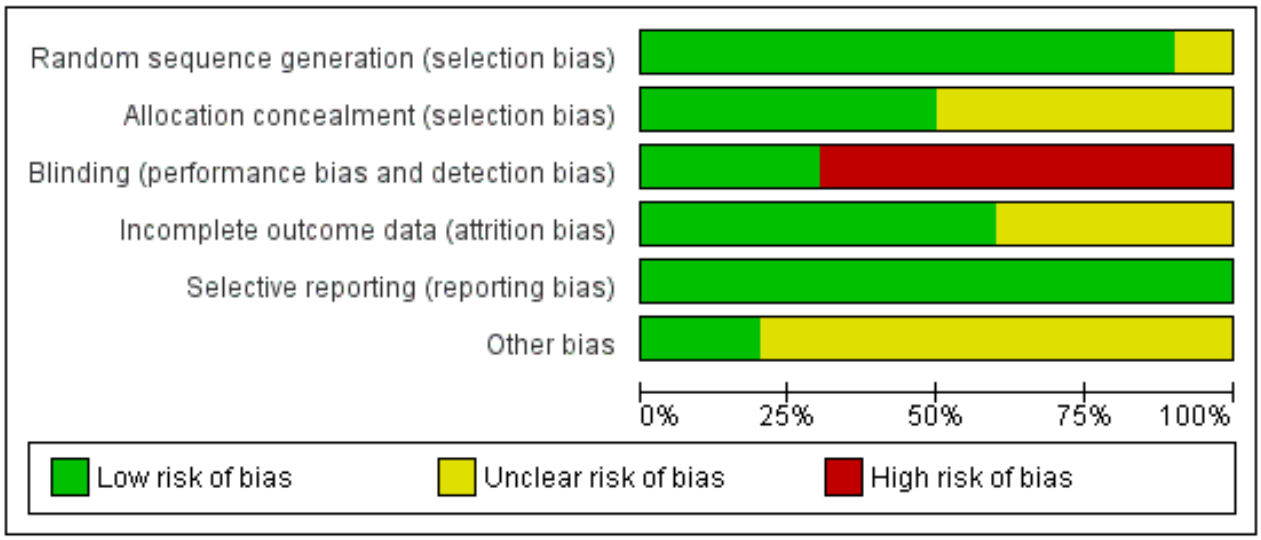
Figure 48. Subgroup analysis EA. Cumulative rankogram comparing each treatment for menstrual bleeding (PBAC) reduction. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface underneath the curve is a cumulative ranking line (SUCRA); the larger the SUCRA the higher its rank among all available treatments.



- The best treatment in the subanalysis of endometrial resection and ablation techniques for bleeding improvement was microwave NREA (SUCRA 80%, mean rank 2.0, OR 1.57, 95% CI 1.03 to 2.39; low certainty evidence).
- Second, bipolar NREA (SUCRA 70%, mean rank 2.9, OR 1.33, 95% CI 0.76 to 2.31; very low certainty evidence).
- Third, other NREA (SUCRA 70%, mean rank 3.0, OR 1.51, 95% CI 0.90 to 2.53; very low certainty evidence).
- Fourth, other REA (SUCRA 60%, mean rank 3.4, OR 1.24, 95% CI 0.43 to 3.61; very low certainty evidence).
- Fifth, TCRE/rollerball (SUCRA 40% and mean rank 4.5, reference comparator).
- Sixth, hydrothermal ablation (SUCRA 20%, mean rank 5.9, OR 0.72, 95% CI 0.37 to 1.41; very low certainty evidence).
- Worst, balloon NREA (SUCRA 10%, mean rank 6.3, OR 0.64, 95% CI 0.39 to 1.05; very low certainty evidence).

Figure 49 summarises the risk of bias of trials contributing data to the NMA. All trials were at either low or unknown risk of bias for all types of bias except blinding bias, as 65% of the trials were at high risk of performance and detection bias. The lack of blinding could have influenced bleeding improvement.

Figure 49. Subgroup analysis EA. Risk of bias of trials contributing with direct evidence for bleeding (PBAC) improvement.

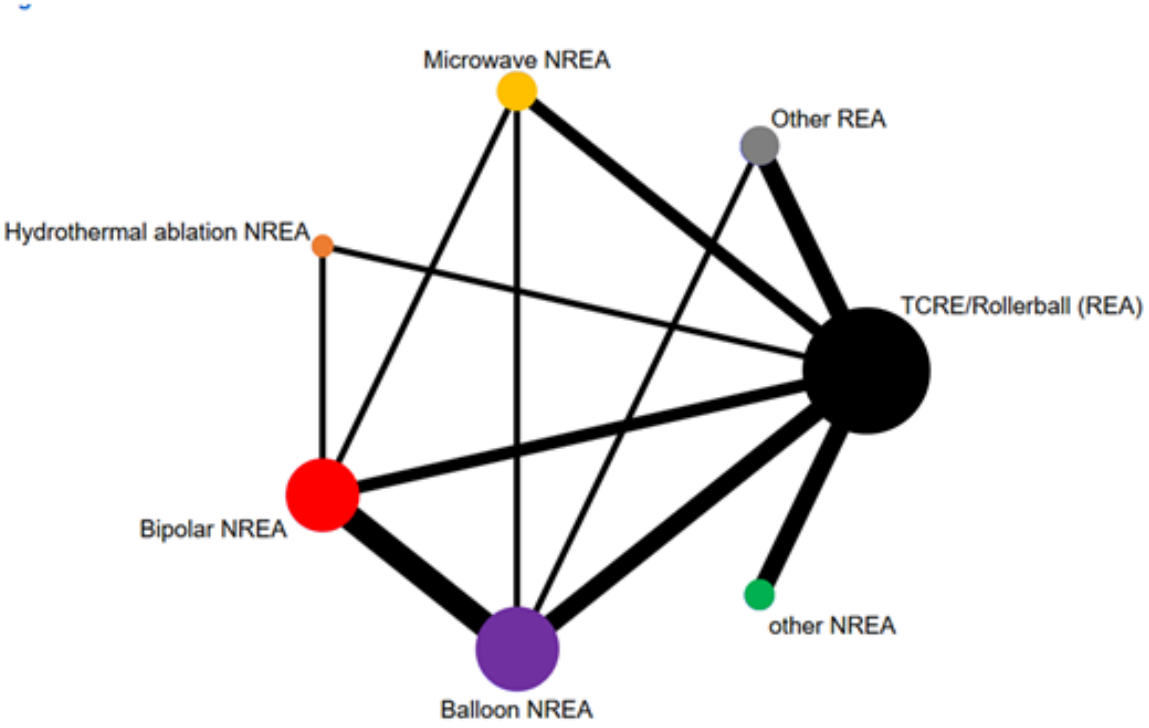


Amenorrhoea (subgroup EA)

Twenty-two studies reported menorrhoea at one year follow-up, comparing seven interventions: TCRE with or without rollerball, other REA, microwave NREA, hydrothermal ablation NREA, bipolar NREA, ballooon NREA and other NREA. See Table 21 for the summary of findings table for this outcome.

The network is connected: Figure 50 presents the NMA diagram for amenorrhoea.

Figure 50. Subgroup analysis EA. Network: women with amenorrhoea at one year follow-up. The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Multiarm trials contribute to more than one comparison.



We used the random-effects model, as a Tau value of 0.88 suggests moderate/large heterogeneity in the log-odds ratio scale, and there was evidence of inconsistency using the node-split model for comparisons (microwave NREA versus bipolar NREA and bipolar NREA versus balloon NREA). Evidence for inconsistency was unclear using the inconsistency model (P = 0.089), with a Tau of 0.76, which is lower than for the consistency model and suggests some inconsistency. Results should be interpreted with caution. See consistency details in Appendix 15.

See the forest plot in Figure 51.

Figure 51. Subgroup EA. Forest plot for amenorrhoea. Colours of the lines are according to the certainty of the evidence: dark green, high certainty evidence (HCE); light green, moderate certainty evidence (MCE); yellow, low certainty evidence (LCE); and red, very low certainty evidence (VLCE).

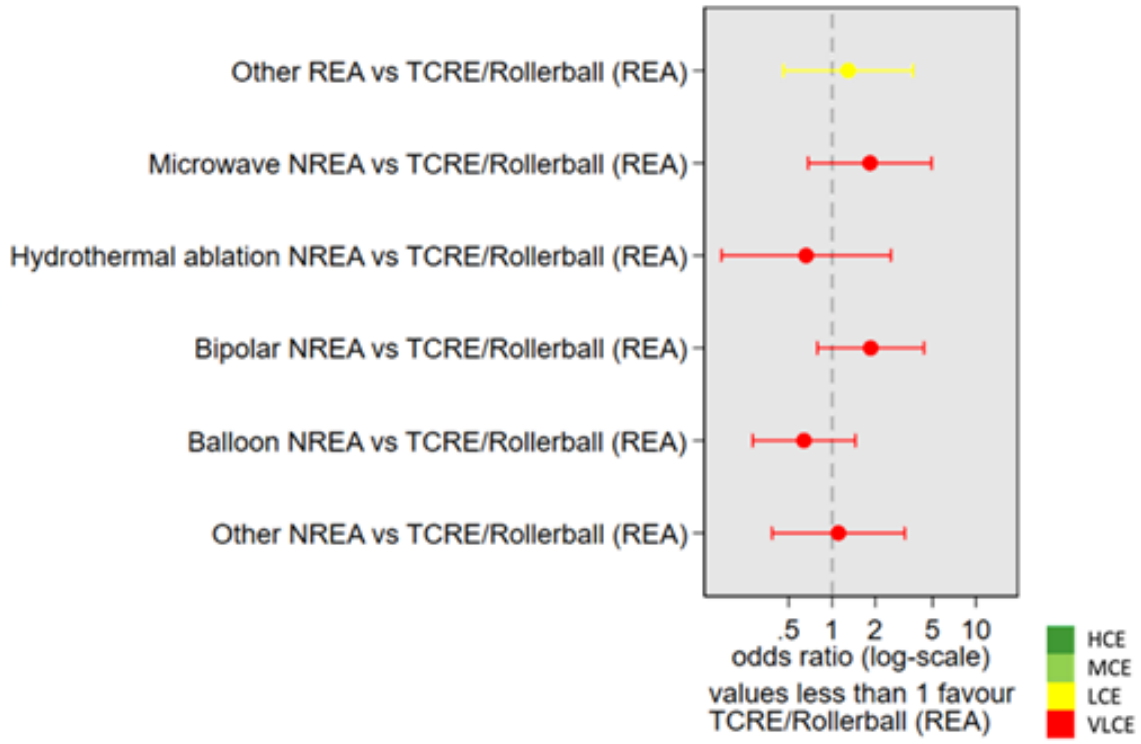
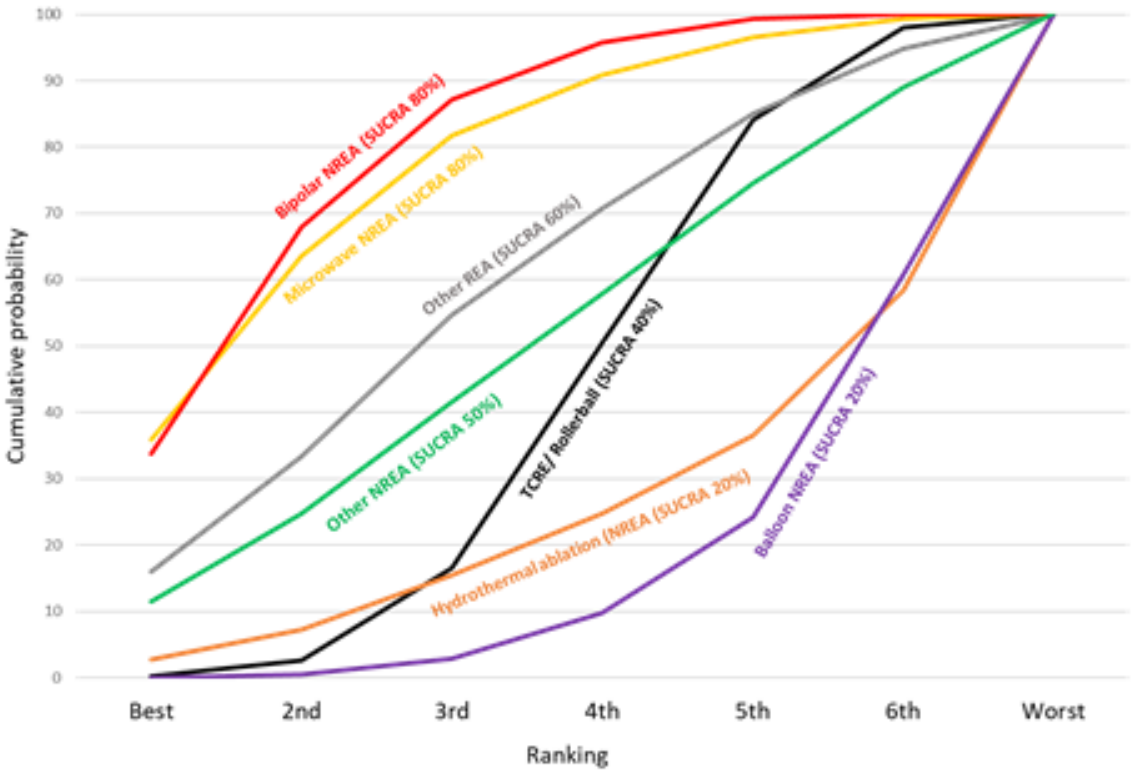


Figure 52 shows the cumulative probabilities for each treatment at each possible rank for achieving amenorrhoea at one year follow-up.

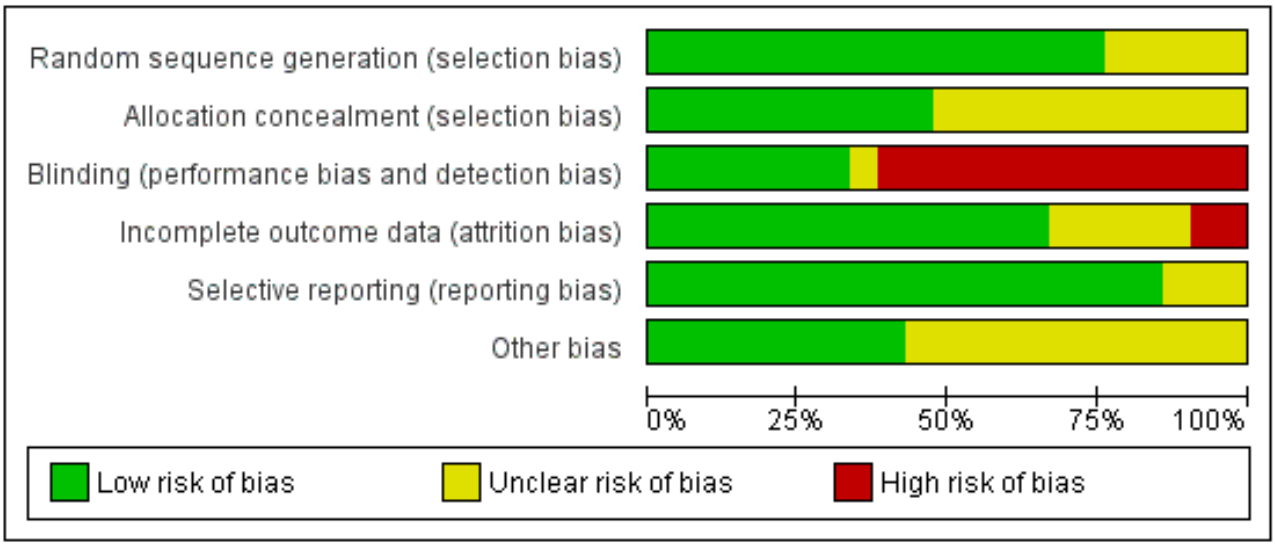
Figure 52. Subgroup analysis EA. Cumulative rankogram comparing each treatment amenorrhoea at one year follow-up. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface underneath the curve is a cumulative ranking line (SUCRA); the larger the SUCRA the higher its rank among all available treatments.



- The best treatment among endometrial resection and ablation techniques for achieving amenorrhoea at one year follow-up is bipolar NREA (SUCRA 80%, mean rank 2.2, OR 1.86, 95% CI 0.79 to 4.36; very low certainty evidence).
- Second, microwave NREA (SUCRA 80%, mean rank 2.3, OR 1.84, 95% CI 0.69 to 4.93; very low certainty evidence).
- Third, other REA (SUCRA 60%, mean rank 3.5, OR 1.30, 95% CI 0.46 to 3.69; very low certainty evidence).
- Fourth, other NREA (SUCRA 50%, mean rank 4.0, OR 1.11, 95% CI 0.38 to 3.20; very low certainty evidence).
- Fifth, TCRE/rollerball (SUCRA 40%, mean rank 4.5, reference comparator).
- Sixth, hydrothermal ablation (SUCRA 20%, mean rank 5.6, OR 0.66, 95% CI 0.17 to 2.56; very low certainty evidence).
- Worst, balloon NREA (SUCRA 20%, mean rank 6.0, OR 0.64, 95% CI 0.28 to 1.45; very low certainty evidence).

Figure 53 summarises the risk of bias of trials contributing data to the NMA. All trials were at either low or unknown risk of selection bias (random sequence generation and allocation concealment), reporting and other bias, but 60% were at high risk of performance and detection bias (blinding). We are uncertain whether the lack of blinding may influence the perception of amenorrhoea.

Figure 53. Subgroup analysis EA. Risk of bias amenorrhoea at one year follow-up.

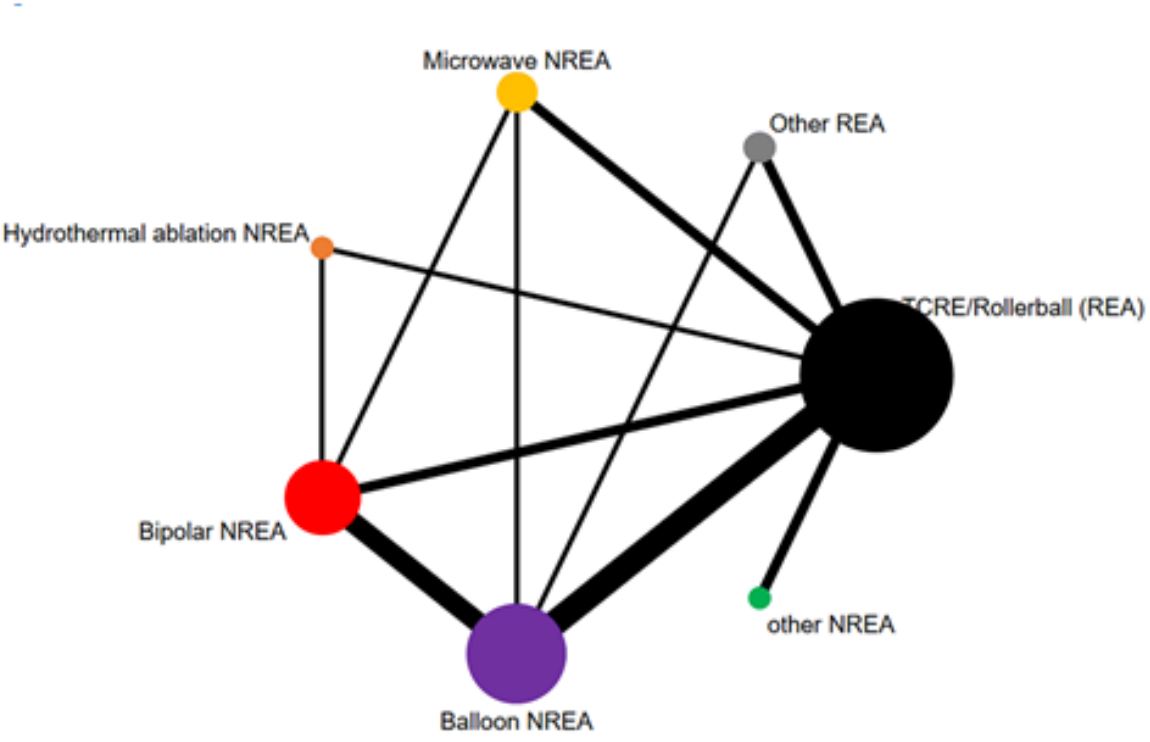


2. Satisfaction (subgroup EA)

Twenty-seven studies reported satisfaction at one year follow-up, comparing seven interventions: TCRE with or without rollerball, other REA, microwave NREA, hydrothermal ablation NREA, bipolar NREA, balloon NREA and other NREA. See Table 22 for the summary of findings table for this outcome.

The network is connected: Figure 54 presents the NMA diagram for satisfaction.

Figure 54. Subgroup analysis EA. Network: satisfaction at one year follow-up.The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Multiarm trials contribute to more than one comparison.



We used the fixed-effect model. There is no evidence of inconsistency using node-split or inconsistency models (P value for inconsistency 0.49). See consistency details in Appendix 16.

See forest plot is in Figure 55.

Figure 55. Subgroup analysis EA. Forest plot satisfaction. Colours of the lines are according to the certainty of the evidence: dark green, high certainty evidence (HCE); light green, moderate certainty evidence (MCE); yellow, low certainty evidence (LCE); and red, very low certainty evidence (VLCE).

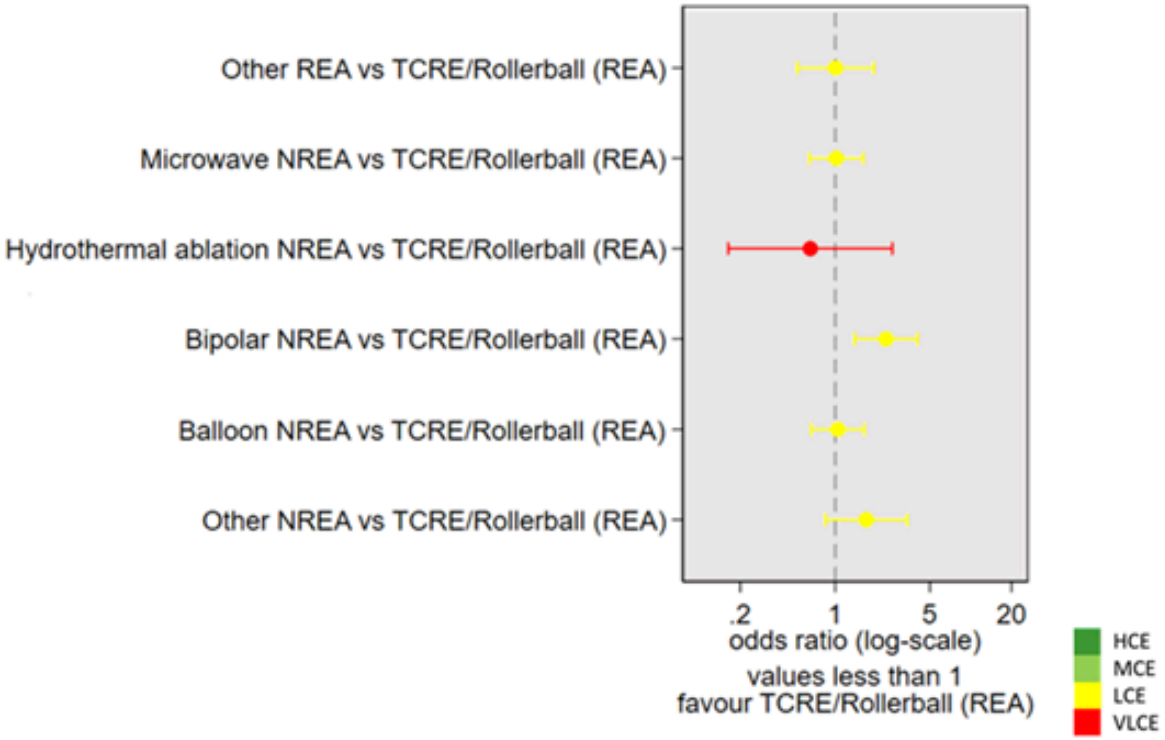
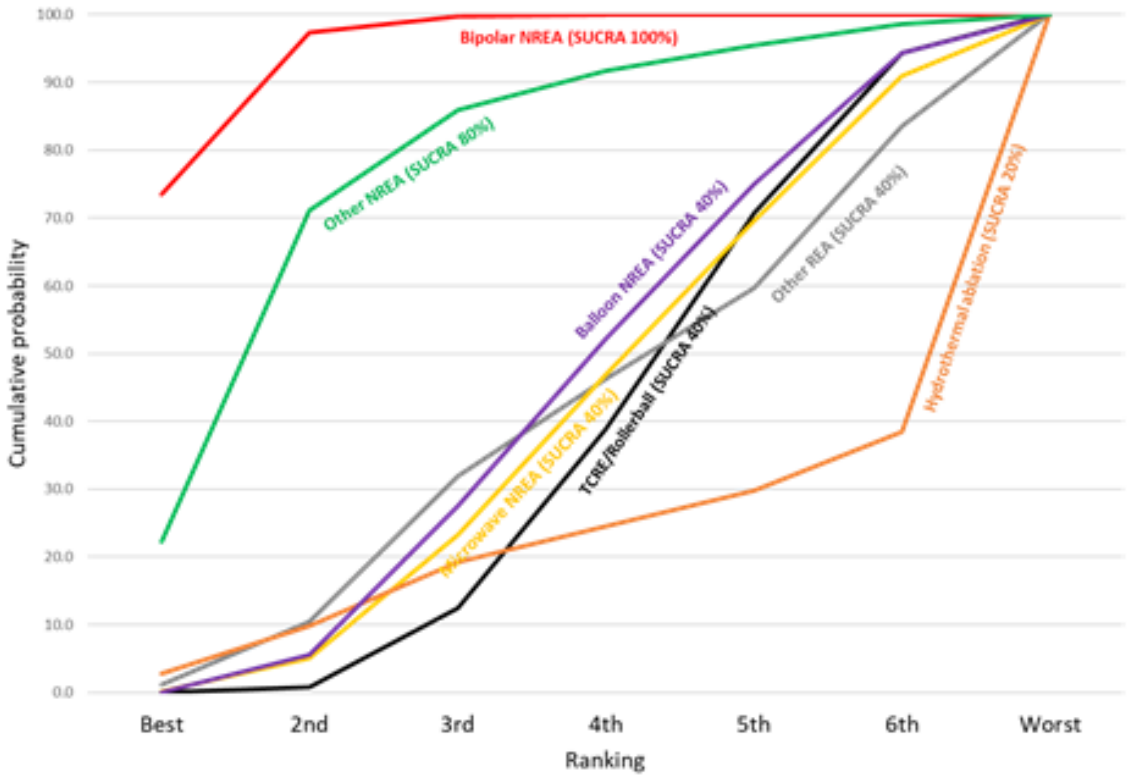


Figure 56 shows the cumulative probabilities for each treatment at each possible rank for achieving amenorrhoea at one year follow-up.

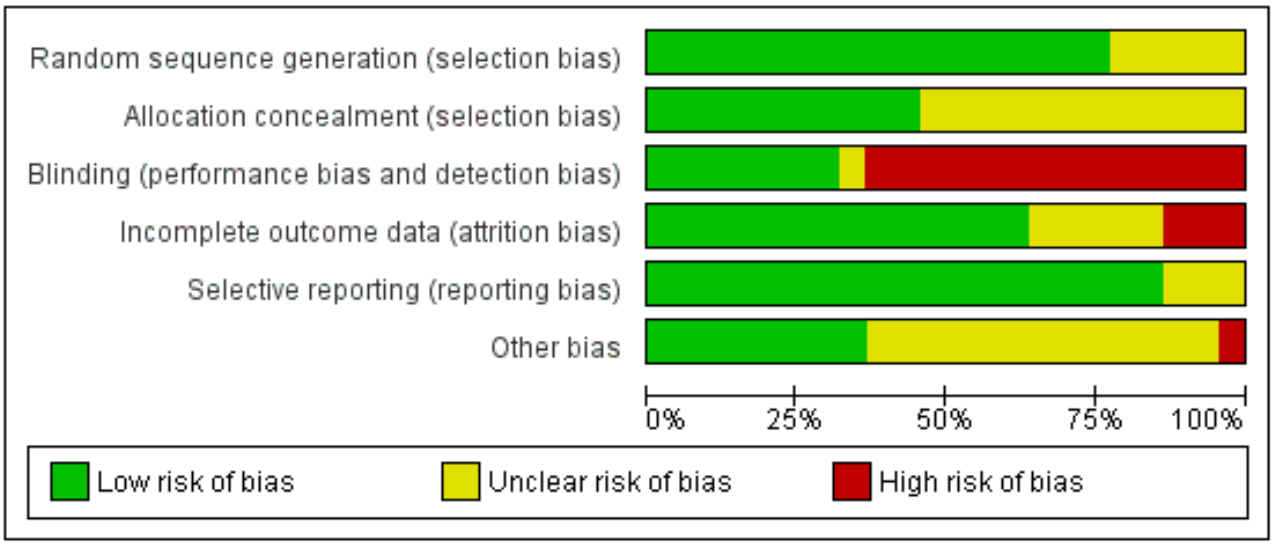
Figure 56. Subgroup analysis EA. Cumulative rankogram comparing each treatment for satisfaction. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface underneath the curve is a cumulative ranking line (SUCRA); the larger the SUCRA the higher its rank among all available treatments.



- The best treatment in the subanalysis of endometrial resection and ablation techniques for satisfaction is bipolar NREA (SUCRA 100%, mean rank 1.3, OR 2.37, 95% CI 1.39 to 4.05; low certainty evidence).
- Second, other NREA (SUCRA 80%, mean rank 2.3, OR 1.70, 95% CI 0.85 to 3.40; low certainty evidence).
- Third, balloon NREA (SUCRA 40%, mean rank 4.5, OR 1.05, 95% CI 0.67 to 1.64; low certainty evidence).
- Fourth, microwave NREA (SUCRA 40%, mean rank 4.6, OR 1.02, 95% CI 0.69 to 1.61; low certainty evidence).
- Fifth, other REA (SUCRA 40%, mean rank 4.7, OR 1.01, 95% CI 0.53 to 1.93; low certainty evidence).
- Sixth, TCRE/rollerball (SUCRA 40%, mean rank 4.8, reference comparator).
- Worst, hydrothermal ablation (SUCRA 20%, mean rank 5.5, OR 0.66, 95% CI 0.16 to 2.64; very low certainty evidence).

Figure 57 summarises the risk of bias of trials contributing data to the NMA. All trials were at either low or unknown risk of selection bias (random sequence generation and allocation concealment) and reporting bias, but 60% were at high risk of performance and detection bias (blinding). We are uncertain whether the lack of blinding may influence the perception of amenorrhoea. The risk of attrition and other bias was low or unknown in 80% of the trials.

Figure 57. Subgroupanalysis EA. Risk of bias of trials contributing with direct evidence for Satisfaction.



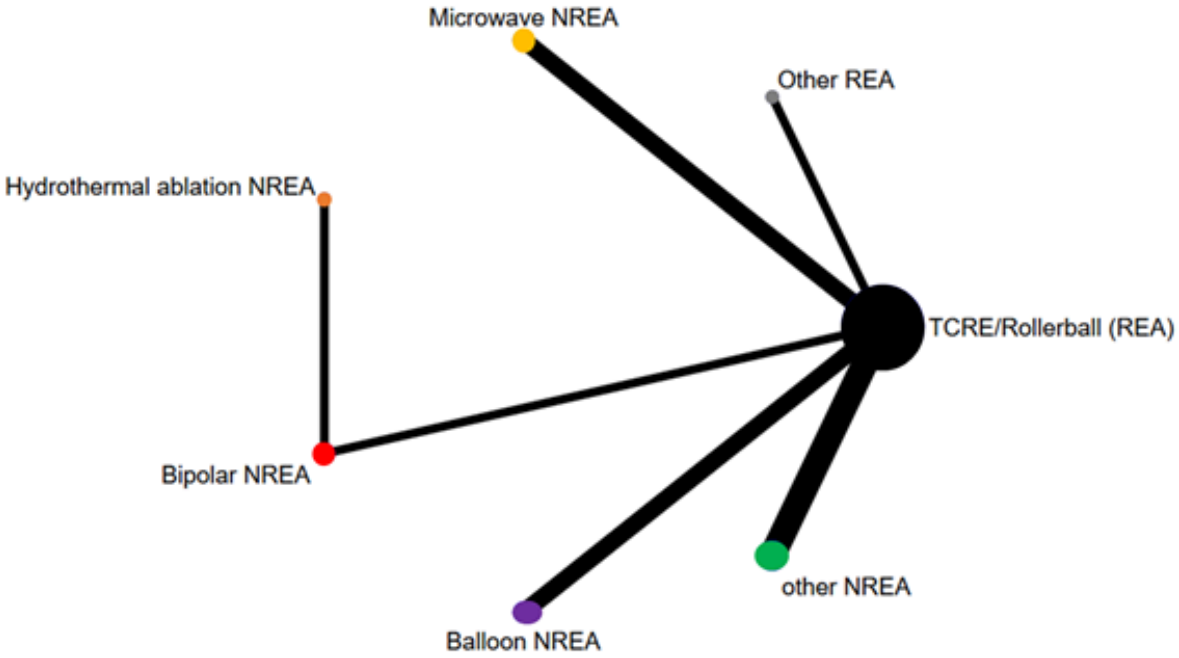
3. Adverse events (subgroup EA)

There were no data available for any adverse event.

Perforation

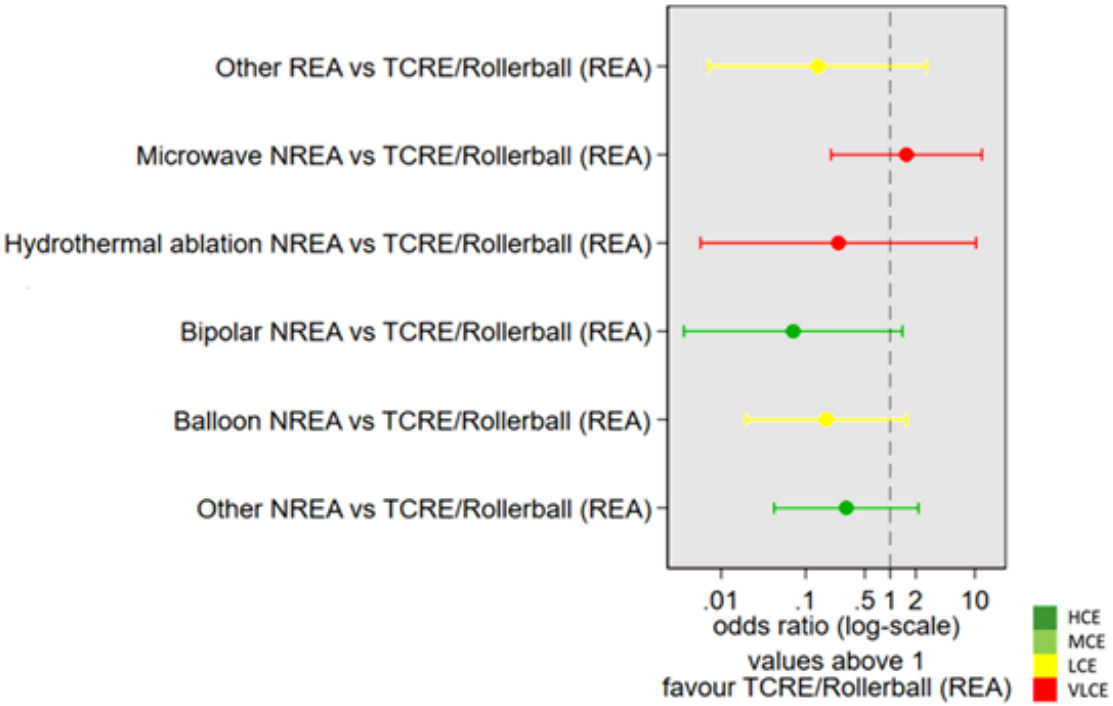
Nine studies reported perforation, comparing seven treatments: TCRE with or without rollerball, other REA, microwave NREA, hydrothermal ablation NREA, bipolar NREA, balloon NREA and other NREA. See Table 23 for the summary of findings table for this outcome. The network was connected; see Figure 58 for network diagram.

Figure 58. Subgroup analysis EA. Subnetwork connected. Perforation. The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Multiarm trials contribute to more than one comparison.



See forest plot in Figure 59.

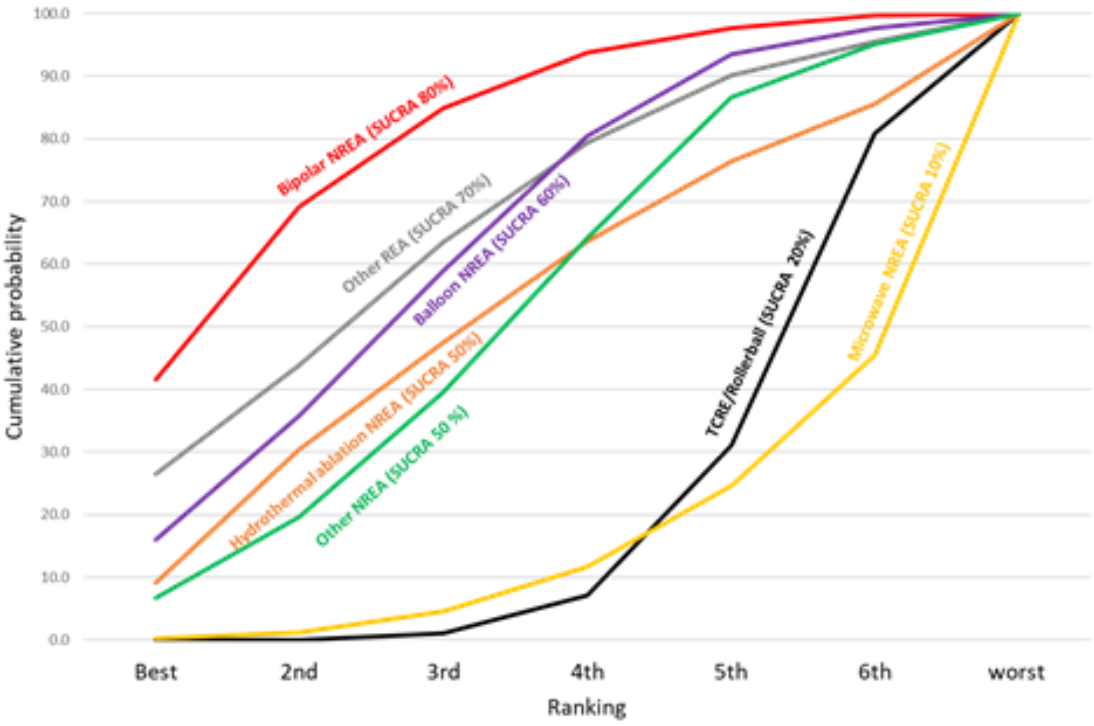
Figure 59. Subgroup analysis EA. Forest plot for perforation. Colours of the lines are according to the certainty of the evidence: dark green, high certainty evidence (HCE); light green, moderate certainty evidence (MCE); yellow, low certainty evidence (LCE); and red, very low certainty evidence (VLCE).



We used the fixed-effect model. There is potential for inconsistency as there were no loops in the network.

Figure 60 shows the cumulative probabilities for each treatment at each possible rank for perforation (lower rate of perforation has a higher rank).

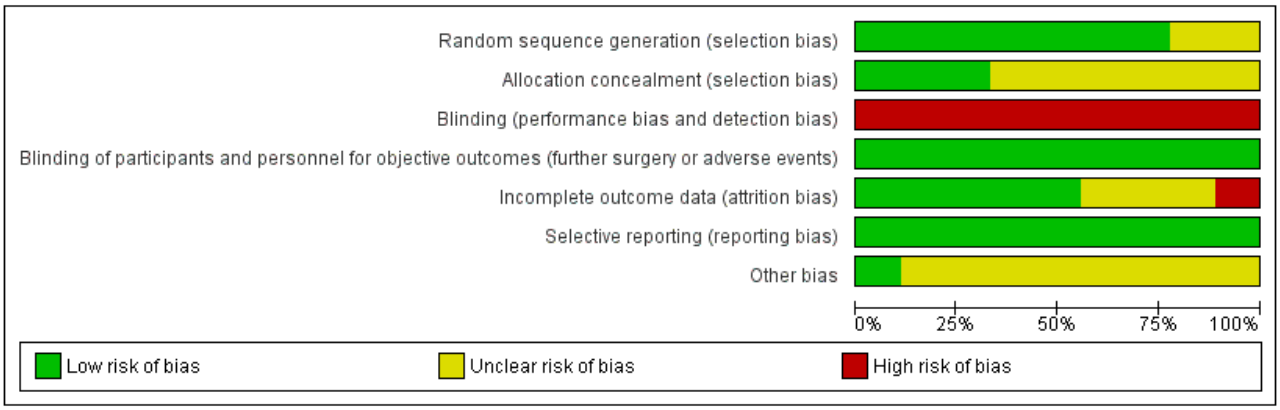
Figure 60. Subgroup analysis EA.Cumulative rankogram comparing each treatment for perforation. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface underneath the curve is a cumulative ranking line (SUCRA); the larger the SUCRA the higher its rank among all available treatments.. Higher rank reflects a lower chance of perforation.



- The best treatment in the subanalysis of endometrial resection and ablation techniques for perforation (lower rate) was bipolar NREA (SUCRA 80%, mean rank 2.1, OR 0.07, 95% CI 0.00 to 1.39; moderate certainty evidence).
- Second, other REA (SUCRA 70%, mean rank 3.0, OR 1.40, 95% CI 0.01 to 2.71; low certainty evidence).
- Third, balloon NREA (SUCRA 60%, mean rank, 3.2, OR 0.30, 95% CI 0.04 to 2.16; low certainty evidence).
- Fourth, other NREA (SUCRA 50%, mean rank 3.9, OR 0.19, 95% CI 0.38 to 1.00; moderate certainty evidence).
- Fifth, hydrothermal ablation NREA (SUCRA 50%, mean rank 3.9, OR 0.24, 95% CI 0.01 to 10.38; very low certainty evidence).
- Sixth, TCRE/rollerball (SUCRA 20%, mean rank 5.8, reference comparator).
- Worst, microwave NREA (SUCRA 10%, mean rank 6.1, OR 1.55, 95% CI 0.20 to 12.12; very low certainty evidence).

Figure 61 summarises the risk of bias of trials contributing data to the NMA. All trials were at either low or unknown risk of selection bias (random sequence generation and allocation concealment), reporting and other bias, but they were all at high risk of performance and detection bias (blinding). The lack of blinding probably did not influence the diagnosis of perforation, but we cannot be certain. The risk of attrition bias was low or unknown in 90% of trials.

Figure 61. Subgroup analysis EA. Risk of bias of trials contributing with direct evidence to perforation.



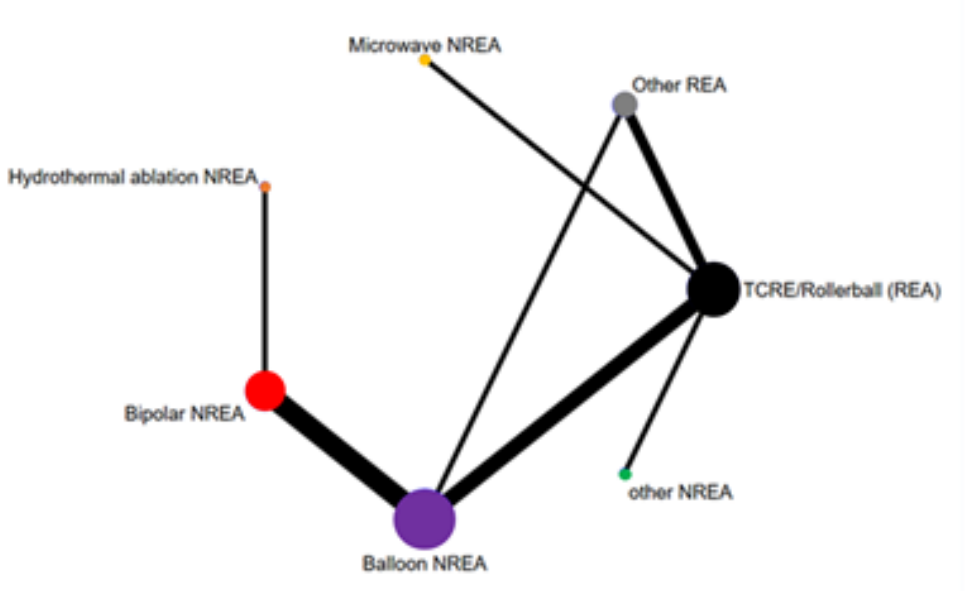
4. Requirement of further surgery for HMB (subgroup EA)

Requirement of any surgery for HMB treatment (endometrial ablation/ resection or hysterectomy), subgroup EA

Thirteen studies reported the requirement of any further hysterectomy to treat persistent HMB, comparing seven treatments: TCRE with or without rollerball, other REA, microwave NREA, hydrothermal ablation NREA, bipolar NREA, balloon NREA and other NREA. See Table 24 for the summary of findings table for this outcome.

The network is connected. See Figure 62 for the network diagram.

Figure 62. Subgroup analysis EA. Network: requirement of further surgery (ablation or hysterectomy) for HMB.The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Multiarm trials contribute to more than one comparison.



There is no evidence of inconsistency using the node-split or inconsistency model (P value for inconsistency 0.97). See Appendix 17.

See the forest plot in Figure 63. Figure 64 presents the cumulative probabilities for each treatment at each possible rank for requirement of further surgery for HMB at up to one year follow-up.

Figure 63. Subgroup analysis EA. Forest plot for requirement of any further surgery for HMB treatment. Colours of the lines are according to the certainty of the evidence: dark green, high certainty evidence (HCE); light green, moderate certainty evidence (MCE); yellow, low certainty evidence (LCE); and red, very low certainty evidence (VLCE).

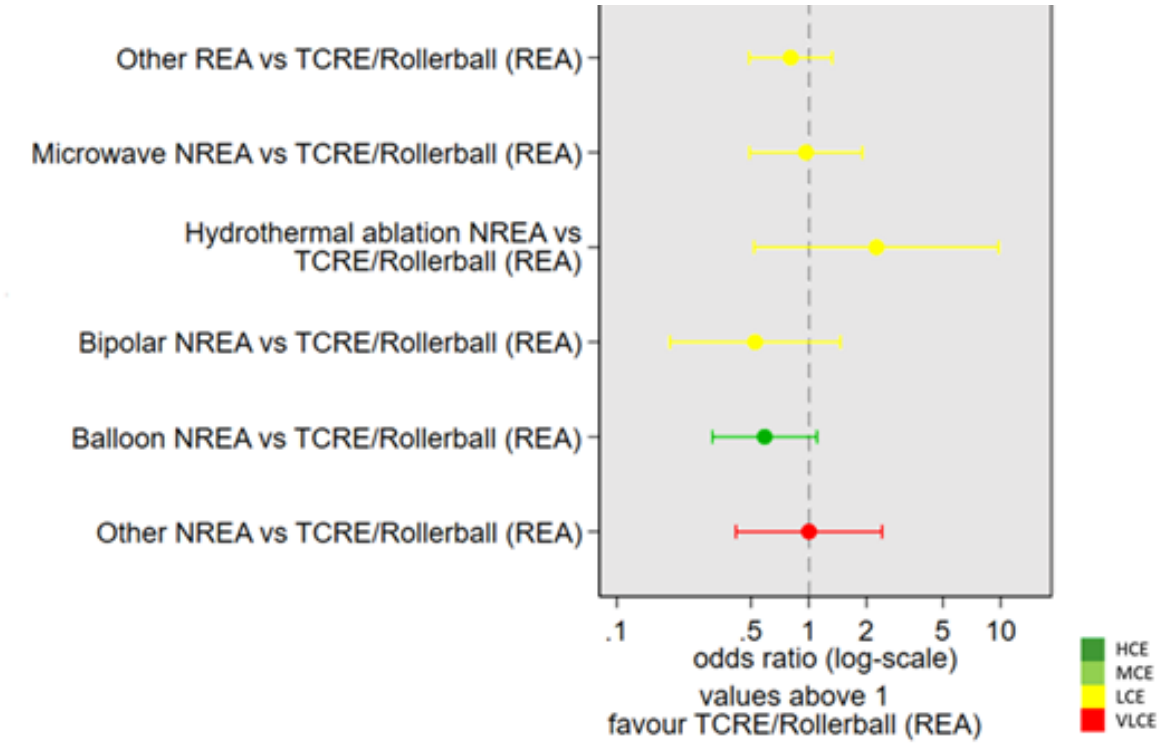
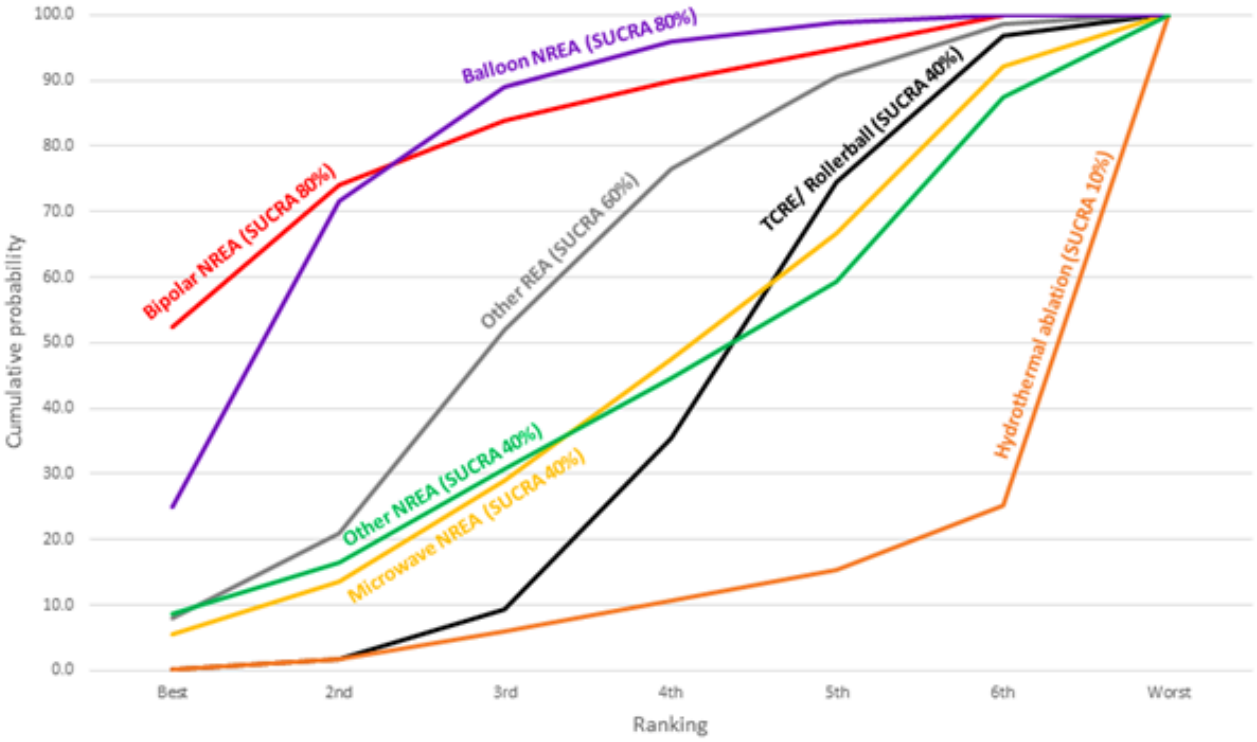


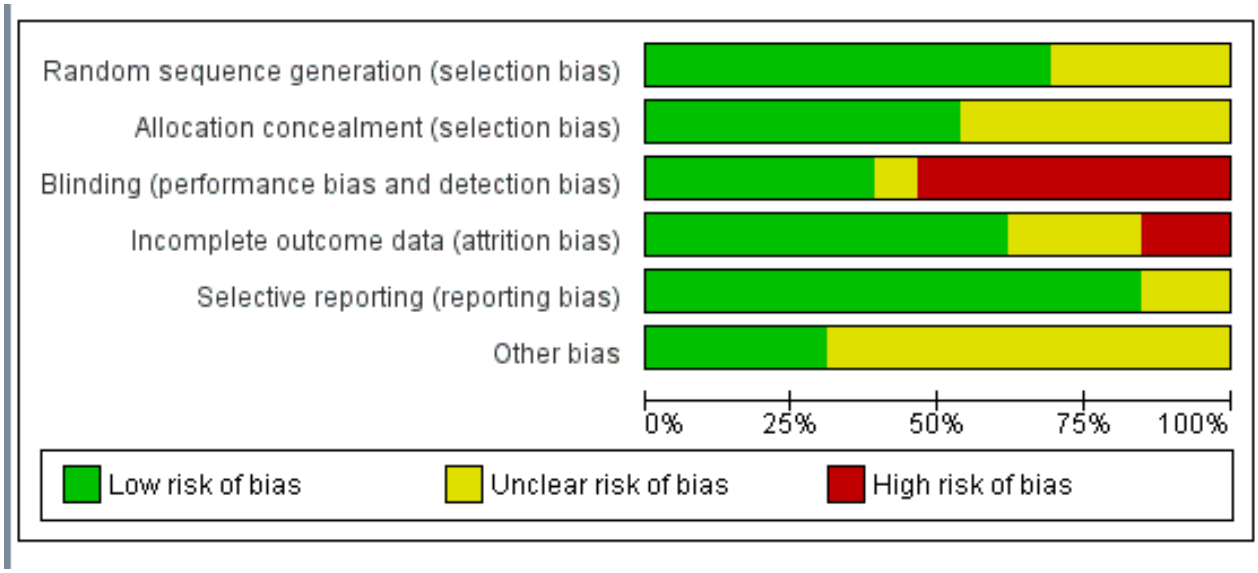
Figure 64. Subgroup analysis EA. Cumulative rankogram comparing each treatment for requirement of further surgery for HMB treatment. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface underneath the curve is a cumulative ranking line (SUCRA); the larger the SUCRA the higher its rank among all available treatments.



- The best treatment in the subanalysis of endometrial resection and ablation techniques for requirement of further surgery (endometrial ablation or hysterectomy) for persistent bleeding (lower rate) was bipolar NREA (SUCRA 80%, mean rank 2.1, OR 0.52, 95% CI 0.19 to 1.46; low certainty evidence).
- Second, balloon NREA (SUCRA 80%, mean rank 2.2, OR 0.59, 95% CI 0.31 to 1.10; moderate certainty evidence).
- Third, other REA (SUCRA 60%, mean rank 3.5, OR 0.80, 95% CI 0.49 to 1.32; very low certainty evidence).
- Fourth and fifth (tied), microwave NREA (SUCRA 40%, mean rank 4.5, OR 0.97, 95% CI 0.49 to 1.90; low certainty evidence) and other NREA (SUCRA 40%, mean rank 4.5, OR 1.00, 95% CI 0.42 to 2.40; very low certainty evidence).
- Sixth, TCRE/rollerball (SUCRA 40% mean rank 4.8, reference comparator).
- Worst, hydrothermal ablation (SUCRA 10%, mean rank 6.4, OR 2.25, 95% CI 0.52 to 9.77; low certainty evidence).

Figure 65 summarises the risk of bias of trials contributing with data to the NMA. All trials were at either low or unknown risk of bias for all types of bias except blinding and attrition. Over half were at high risk of blinding bias, and 80% were at low or unclear risk of attrition bias. The lack of blinding is not likely to influence the requirement of further surgery for persistent bleeding.

Figure 65. Subgroup analysis EA. Risk of bias of trials contributing with direct evidence to any further surgery for HMB treatment.

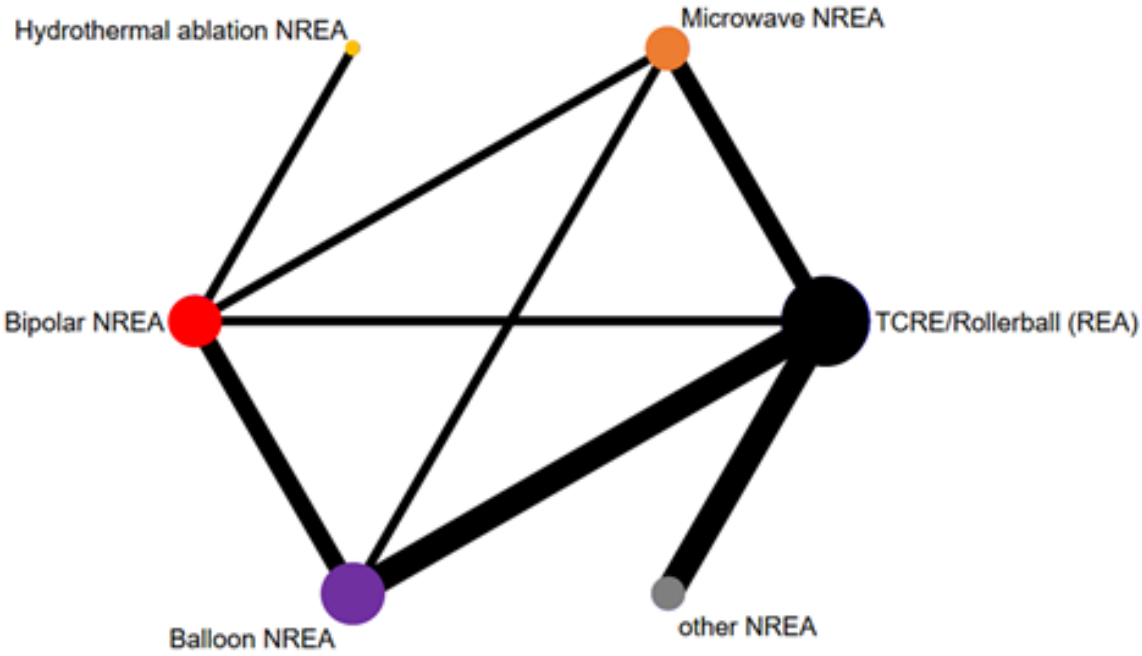


Requirement of further hysterectomy for HMB treatment (subgroup EA)

Fourteen studies reported the requirement of further hysterectomy to treat persistent HMB, comparing six treatments: TCRE with or without rollerball, microwave NREA, hydrothermal ablation NREA, bipolar NREA, ballooon NREA and other NREA. See Table 25 for the summary of findings table for this outcome.

The network was connected. See Figure 66 for network diagram.

Figure 66. Subgroup analysis EA. Network: requirement of further hysterectomy for HMB. The nodes represent an intervention, and their size is proportional to the number of trials comparing this intervention to any other intervention in the network. The lines connecting each pair of interventions represent a direct comparison and are drawn proportional to the number of trials making each direct comparison. Multiarm trials contribute to more than one comparison.



We used the fixed-effect model. There is no evidence of inconsistency using node-split or inconsistency modelw (P value for inconsistency 0.7). See Appendix 18 for details.

See the forest plot in Figure 67. Figure 68 presents the cumulative probabilities for each treatment at each possible rank for requirement of further hysterectomy for HMB treatment at one year follow-up.

Figure 67. Subgroup EA. Forest plot requirement of further hysterectomy for HMB. Colours of the lines are according to the certainty of the evidence: dark green, high certainty evidence (HCE); light green, moderate certainty evidence (MCE); yellow, low certainty evidence (LCE); and red, very low certainty evidence (VLCE).

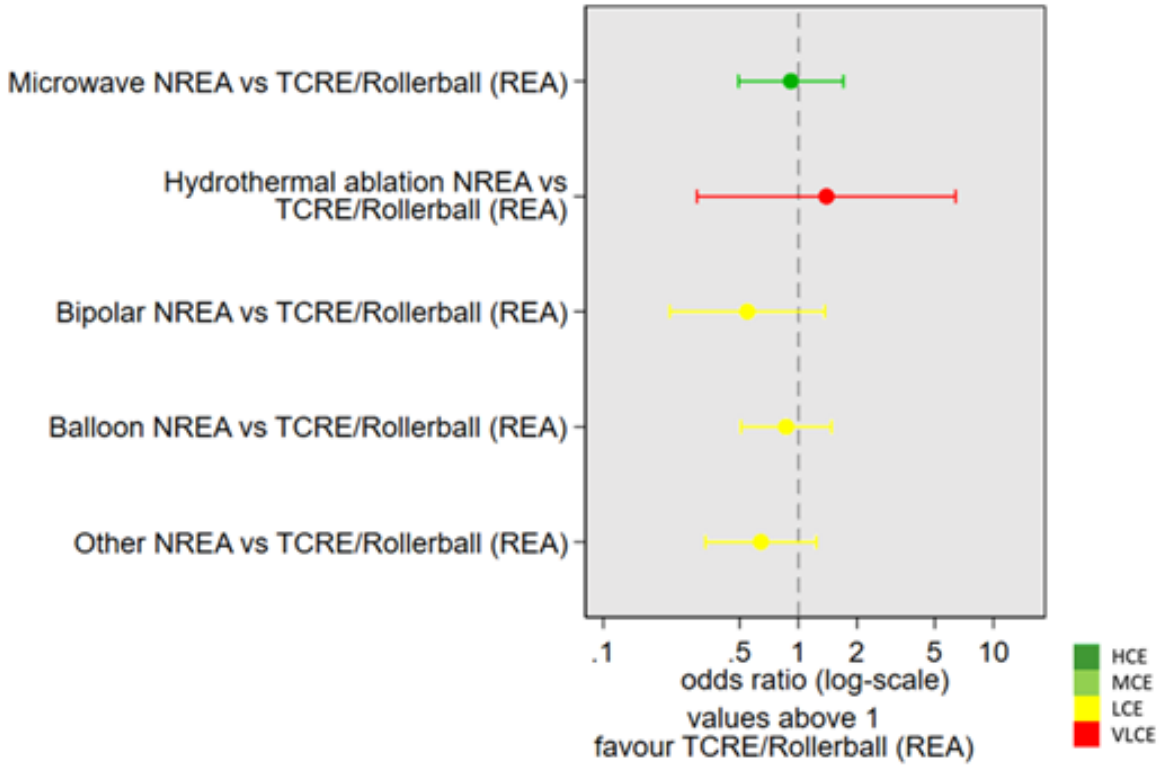
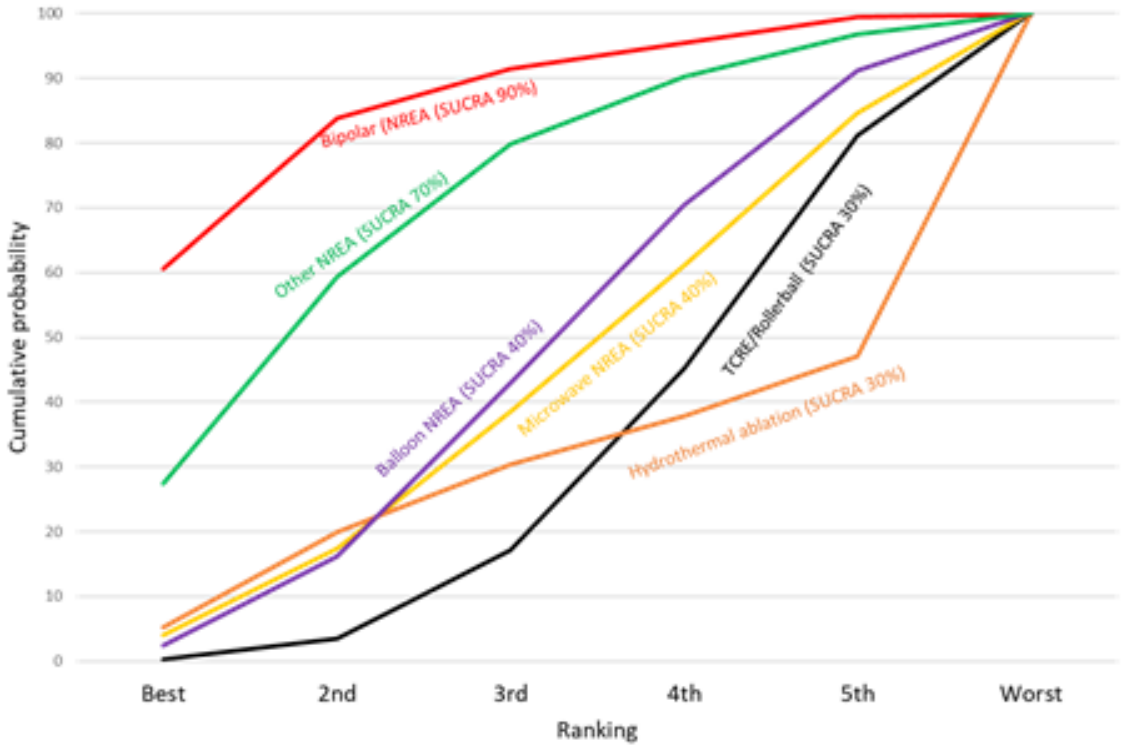


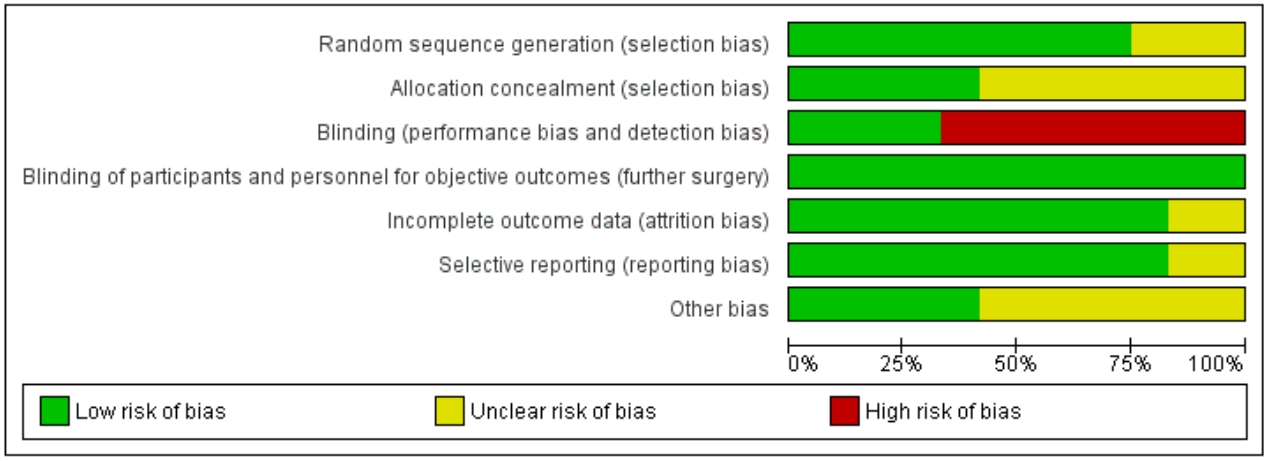
Figure 68. Subgroup analysis EA. Cumulative rankogram comparing each treatment for requirement of further hysterectomy for HMB. Ranking indicates the cumulative probability of being the best treatment, the second best, the third best, etc. The x axis shows the relative ranking and the y-axis, the cumulative probability of each ranking. The surface underneath the curve is a cumulative ranking line (SUCRA); the larger the SUCRA the higher its rank among all available treatments.



- The best treatment in the subanalysis of endometrial resection and ablation techniques for requirement of further hysterectomy for persistent bleeding (lower rate) was bipolar NREA (SUCRA 80%, mean rank 1.9, OR 0.55, 95% CI 0.22 to 1.37; low certainty evidence).
- Second, other REA (SUCRA 70%, mean rank 2.3, OR 0.64, 95% CI 0.33 to 1.23; low certainty evidence).
- Third, balloon NREA (SUCRA 50%, mean rank 3.6, OR 0.86, 95% CI 0.51 to 1.48; low certainty evidence).
- Fourth, microwave NREA (SUCRA 40%, mean rank 3.9, OR 0.92, 95% CI 0.49 to 1.70; moderate certainty evidence).
- Fifth, TCRE/rollerball (SUCRA 30%, mean rank 4.5, reference comparator).
- Sixth, hydrothermal ablation (SUCRA 20%, mean rank 4.9, OR 1.39, 95% CI 0.30 to 6.41; very low certainty evidence).

Figure 69 summarises the risk of bias of trials contributing with data to the NMA. All trials were at either low or unknown risk of all biases except blinding. However, the lack of blinding is not likely to influence the requirement of further hysterectomy for persistent bleeding.

Figure 69. Subgroup analysis EA. Risk of bias of trials contributing with direct evidence to further hysterectomy for HMB.



DISCUSSION

Summary of main results

This overview included nine Cochrane Reviews (covering 104 studies) of interventions to treat heavy menstrual bleeding (HMB) in women of reproductive age. Eighty-five of these studies (9950 participants) provided direct evidence for the overview network meta-analysis (NMA). The overview shows that first-line treatments for HMB vary widely in efficacy, safety and satisfaction, while the differences are less pronounced for second-line treatments. We assessed the certainty of the evidence for specific interventions as being from moderate to very low, with most being low to very low certainty.

First-line treatments

For women with HMB, evidence suggests LNG-IUS is the best intervention to reduce menstrual blood loss. Antifibrinolytics are probably second-best. Evidence suggests that long-cycle progestogens reduce menstrual blood loss, and NSAIDs slightly reduce HMB; we are uncertain of the true effect of the remaining interventions, such as combined oral contraceptives (COC), combined vaginal ring (CVR), cyclical luteal progestogens and ethamsylate, as the evidence was very low certainty; see Table 5.

The sensitivity analysis for mean blood loss (without combining data, see Table 6), the perception of bleeding improvement (Table 7), and satisfaction (Table 8) provided very low certainty evidence; thus, we are uncertain of the true effect of the interventions for these outcomes.

The evidence suggests that there is little to no difference in quality of life improvement when comparing tranexamic acid versus long-cycle progestogens, or comparing LNG-IUS versus COC. We are uncertain of the true effect on quality of life when comparing antifibrinolytics versus short-cycle progestogens (very low certainty evidence; Table 9).

The evidence suggests that the use of antifibrinolytics, NSAIDs, LNG-IUS or placebo results in little to no difference on the rate of any adverse events, and also that COC increases the rate of any side effect. We are uncertain of the true effect of the remaining interventions (CVR, luteal and long-cycle progestogens and ethamsylate), as the evidence is very low certainty (Table 10).

There may be little to no difference in serious adverse events between antifibrinolytics and placebo (Table 11).

The evidence suggests that women using an LNG-IUS are less likely to require further treatment for HMB compared to women receiving COC (Table 12).

Second-line treatments

Evidence suggests that hysterectomy of any type is the best intervention to reduce menstrual blood loss (with and without imputed data). NREA probably reduces menstrual blood loss and is the second best (with and without imputed data). Evidence suggests that REA reduces menstrual blood loss without imputed data, but we are uncertain of the true effect with imputed data (very low certainty evidence; Table 13 Table 14).

Evidence on amenorrhoea was of very low certainty, mainly because of very serious risk of bias of the direct evidence and serious or very serious imprecision; thus, we are uncertain of the true effect of the interventions on this outcome (Table 15).

Evidence suggests that minimally invasive hysterectomy (laparoscopic or vaginal) results in a large increase in the proportion of women satisfied with treatment, and NREA results in an increase in the proportion of women satisfied with treatment. We are uncertain of the true effect of the remaining interventions (very low certainty evidence; Table 16).

Women with minimally invasive hysterectomy probably have a better quality of life at up to two years follow-up compared to women receiving NREA. There may be little to no difference in the general health for the following pairwise comparisons: unspecified endometrial ablation (EA) versus hysterectomy (unspecified or at surgeon's discretion), and NREA versus LNG-IUS. The evidence is very uncertain about the effect on quality of life of the following comparisons: REA versus minimally invasive hysterectomy or open hysterectomy, and LNG-IUS versus minimally invasive hysterectomy or open hysterectomy (very low certainty evidence; Table 17).

Evidence on any adverse event was very low certainty, so we are uncertain of the true effect of the interventions on this outcome. This uncertainty may be related to the wide variety of adverse events being reported (Table 18).

Hysterectomy (all routes) and NREA probably reduce the rate of the requirement of further surgery for HMB. We are uncertain of the true effect of REA and unspecified EA (very low certainty evidence; Table 19).

EA subgroup analysis

For women with HMB treated with EA, evidence suggests that microwave NREA is the best option for reducing menstrual blood loss, and bipolar NREA is probably the best option for achieving amenorrhoea. We are uncertain of the true effect of the remaining interventions on these outcomes, as the evidence was very low certainty (Table 20; Table 21).

For the outcome of satisfaction, evidence suggests bipolar NREA has the best satisfaction rate; other REA, microwave NREA, balloon NREA, and other NREA may not be different compared to TCRE/rollerball, and we are uncertain of the true effect of hydrothermal NREA, as the evidence was very low certainty (Table 22).

For the adverse event of perforation, bipolar NREA probably shows little to no difference in the perforation rate compared to TCRE/rollerball. Evidence suggests that REA and balloon NREA are little to no different than TCRE/rollerball in the perforation rate. We are uncertain of the true effect of hydrothermal ablation NREA and microwave NREA (very low certainty evidence; Table 23).

Evidence suggests bipolar NREA lowers the rate of requirement of further surgery for HMB. Balloon NREA probably lowers the rate of requirement of further surgery. Evidence suggests that other REA, microwave NREA and hydrothermal NREA produce little to no difference in the rate of requirement of further surgery compared to TCRE. We are uncertain of the true effect of other REA (Table 24).

Evidence suggests little to no difference in the requirement of further hysterectomy for treating HMB between bipolar NREA, other REA, balloon NREA and TCRE/rollerball; and probably little to no difference between microwave NREA and TCRE/rollerball. We are uncertain of the true effect of hydrothermal NREA (very low certainty evidence; Table 25).

Overall completeness and applicability of evidence

We updated all the reviews whose last search was over 18 months old when we started the overview. We summarised all the data available in the Cochrane Reviews, extracting data by studies. We consider it to be complete, although we acknowledge that our searches may have missed relevant studies, and the evidence had limitations.

This overview provides three sets of network meta-analyses reporting on the relative effectiveness of first and second-line HMB treatments, plus a subgroup analysis by type of endometrial ablation technique, in a coherent and methodologically robust way across clinical outcomes, combining direct and indirect evidence to increase the statistical power and confidence in the results. Most of the trials included in the reviews reported the bleeding outcome, but they did so in a wide variety of ways, limiting our ability to combine them. The network meta-analysis results were mostly consistent, and where there was significant inconsistency, this was likely to be due to unstable estimates from single studies.

We excluded trials where participants' baseline characteristics did not match with the overview, that is, studies that included women with HMB due to an intrauterine device, ovulation disorders, or in treatment with anticoagulant drugs. All trials were carried out in clinical settings.

Most trials compared first-line treatments to placebo, enabling us to set placebo as the reference treatment in the networks. Trials did not compare second-line treatments to placebo or no treatment. We decided to use LNG-IUS as the reference treatment for second-line treatments and TCRE/rollerball as the reference treatment for the subgroup analysis of endometrial ablation techniques.

Unfortunately, we were unable to draw conclusions regarding quality of life, as network meta-analysis was not possible.

Another limitation was that we did not have enough studies to use a funnel plot to explore the possibility of small-study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

We consider the information provided by this overview to be valuable for women with HMB, healthcare providers, and policymakers.

Methodologies for both overviews and NMAs have been developed since the publication of the protocol in 2018. It may be appropriate for the update to consider evolving the overview to a review of interventions, which would facilitate the process by allowing a single search with all the NMA details, instead of updating each review.

Quality of the evidence

We recognise that there is no single established approach for assessing the certainty of the effect estimates generated by the network meta-analysis. We applied the GRADE Working Group method for appraising quality of network evidence. Overall, the evidence presented was low, and our confidence in the effect estimates ranged from very low to low. In general, due to the lack of blinding in most of the trials, and some indirectness arising from small studies, most of the comparisons started at moderate certainty. Either because of wide intervals or inconsistency on the network, or both, we then downgraded them to low or very low certainty.

Potential biases in the overview process

Two overview authors (AL and CF) were involved in one study contributing data to the overview ((D) Talis 2006). They did not participate in data extraction or quality assessment for their study. Several authors have been involved on the reviews providing data for the overview, but they did not participate in the assessment of the quality of the reviews. One review contributing studies to the overview was declared stable in 2007, when the only risk of bias assessed was allocation concealment. The earliest trial included was from 1970, and since then the standard of care and even the HMB diagnosis has changed.

Agreements and disagreements with other studies or reviews

In the first-line treatments network, the LNG-IUS appears to be the best for the outcome of bleeding reduction compared to the remaining interventions. This finding is consistent with the evidence summary reported by NICE 2018b which describes the LNG-IUS as effective or more effective than other treatments for HMB in terms of improving health-related quality of life, treatment satisfaction, discontinuation rates and blood loss. In addition, it is widely used in clinical practice and routinely available within primary care, and it should be the first option for treating HMB in women with no identified pathology.

NICE 2018b did not report on adverse events, but instead on discontinuation of treatment due to adverse events, with NSAIDs and tranexamic acid ranking first (1 to 3) and second (1 to 5), and COC ranking 7 (6 to 7, in a ranking from 1 to 7); danazol was not included in the study. This difference maybe due to the first-line treatments network of this overview using any adverse event as an outcome, which may not reflect the presence of serious adverse events.

With respect to second-line treatments for blood loss, NICE 2018b agreed that for women who do not wish to have pharmacological treatment and who do not want to conserve their fertility, surgical options could be considered as a first-line treatment option, which is similar to the second-line treatment results reporting hysterectomy as the best treatment for menstrual blood reduction and avoiding further surgery. The NICE report used a different division of the endometrial ablation procedures, which made it difficult to compare. In terms of blood loss, they reported that NREA was more effective and had higher satisfaction than REA techniques. The second-line treatment network of this overview reported hysterectomy and NREA as being the two best options for menstrual blood reduction, yielding higher rates of satisfaction and avoiding future surgery for HMB.

Daniels 2012 published a network meta-analysis of EA techniques, including bipolar NREA, microwave NREA, thermal balloon NREA, hydrothermal NREA, laser NREA, cryoablation NREA and REA. The authors assessed bleeding reduction and satisfaction, reporting that bipolar and microwave ablation devices are more effective than thermal balloon and free fluid ablation for treating HMB with NREA devices, which is consistent with the numerical finding of the subgroup analysis for endometrial ablation techniques.

AUTHORS' CONCLUSIONS

Implications for practice

This overview provides up-to-date evidence on HMB treatments. HMB is a condition that affects a significant proportion of women of reproductive age. There is moderate to very low certainty evidence that treatments for HMB are effective and improve satisfaction. It is important to highlight that the best treatment may not be the same for all women. Clinicians should assess the patient characteristics before applying the result of this NMA, starting with the first-line treatments network, and then, in case of treatment failure or in women who have completed their families, moving to the second-line treatments network.

In women who are not candidates for surgery, LNG-IUS is the most effective first-line treatment to reduce menstrual blood loss. LNG-IUS is probably little to no different than placebo in the rate of adverse events, and the requirement for further treatment may be less likely than in women receiving COC. Antifibrinolytics are probably better than placebo at reducing blood loss, with little to no difference in the rate of adverse events. Long-cycle progestogens may be better than placebo at reducing blood loss. Unfortunately, we are unable to draw conclusions about perceived improvement and satisfaction due to very low certainty evidence.

In women who are candidates for surgery, hysterectomy is the most effective second-line treatment for reducing menstrual blood loss and avoiding further surgery for HMB. Minimally invasive hysterectomy may be better than the LNG-IUS for achieving satisfaction. REA and NREA may be better than LNG-IUS at reducing blood loss. NREA may have higher satisfaction rates than LNG-IUS and may have lower rates of further surgery for HMB. Unfortunately, we were unable to pool the wide variety of adverse events reported, and most were specific to one technique.

For endometrial ablation or resection, the certainty of the evidence for bleeding outcomes was mostly very low. Evidence suggests microwave NREA is better than TCRE for reducing blood loss, but it may not be very different in the satisfaction rate or the rate of further surgery. Evidence suggests that other REA produces a higher amenorrhoea rate than TCRE/rollerball, with little to no difference in the rate of satisfaction, perforation rate and requirement for further surgery than TCRE, with or without rollerball. Evidence suggests that bipolar NREA is better than TCRE/rollerball at achieving satisfaction, with little to no difference in perforation rate and a lower requirement of further surgery. Evidence suggests that balloon NREA produces little to no difference in the satisfaction and perforation rate compared to TCRE/rollerball. Balloon NREA probably has a lower requirement of further surgery than TCRE/rollerball. Evidence suggests that other NREA produces similar satisfaction and perforation rates compared to TCRE, with or without rollerball. Other factors such as the ability to use local (as opposed to general anaesthesia), surgical time, and other adverse events (not considered in this network meta-analysis) may influence the decision by clinician and woman regarding their choice of endometrial ablation options for the treatment of heavy menstrual bleeding.

Implications for research

LNG-IUS is the most effective first-line treatment to reduce menstrual blood loss in women requiring contraception, but there is no clear ranking for the remaining options. There is an overlap between contraception and heavy menstrual bleeding treatment, as hormonal contraceptives reduce menstrual blood loss, and in some cases cause amenorrhoea; progestin-only contraceptives (pill, injections and implants) have been used off-label as HMB treatment. Future research should assess the efficacy and safety of progestogen-only contraceptives and compare different preparations of combined hormonal contraceptives for HMB treatment.

Quality of life should be the primary outcome for future research, as the current HMB definition is based on quality of life.

We had difficulties trying to combine data from different studies, as quality of life was reported in a wide range of ways. This

highlights the importance of developing a core outcome set for heavy menstrual bleeding trials that would facilitate more effective analysis, avoid (or restrict) the use of imputed data, and reduce data waste. The COMET initiative (Core Outcome Measures in Effectiveness Trial) has an ongoing project, 'Defining core outcomes for clinical trials of heavy menstrual bleeding. A Core Outcome sets for Gynaecological conditions (COGS) project' that aims to develop a core outcome set covering all the aspects of heavy menstrual bleeding (COMET 2018).

A core outcomes set should also improve the ability to combine quality of life data. There should be specified safety outcomes, encouraging reporting of any adverse event, as it makes it simpler to compare, avoids the risk of double counting and allows fair comparisons. Comparing adverse events between interventions if they are specific to the intervention (as perforation for endometrial ablation and wound infection for hysterectomy) could lead to false conclusions.

Future research should assess interventions that have been used off-label to treat HMB, such as progestin-only contraceptives, and focus on quality of life improvement.

ACKNOWLEDGEMENTS

The authors acknowledge the contribution of Helen Nagels (Managing Editor) at the Cochrane Gynaecology and Fertility Group's editorial base for her time and support. They thank Abha Maheshwari, Selma Mourad, Kirsten Duckitt and Rui Wang for providing peer review comments. They also thank Malcolm Munro for enlightening them about the history of endometrial ablation and Juan Jose Yepes-Nunez for responding to questions about the NMA summary of findings.

REFERENCES

References to included reviews

Beaumont 2007

Beaumont H, Augood C, Duckitt K, Lethaby A. Danazol for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No: CD001017. [DOI: 10.1002/14651858.CD001017.pub2]

Bofill Rodriguez 2019a

Bofill Rodriguez M, Lethaby A, Grigore M, Brown J, Hickey M, Farquhar C. Endometrial resection and ablation techniques for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews* 2019, Issue 1. Art. No: CD001501. [DOI: 10.1002/14651858.CD001501.pub5]

Bofill Rodriguez 2019b

Bofill Rodriguez M, Lethaby A, Low C, Cameron I. Cyclical progestogens for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews* 2019, Issue 8. Art. No: CD001016. [DOI: 10.1002/14651858.CD001016.pub3]

Bofill Rodriguez 2019c

Bofill Rodriguez M, Lethaby A, Farquhar C. Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews* 2019, Issue 9. Art. No: CD000400. [DOI: 10.1002/14651858.CD000400.pub4]

Bofill Rodriguez 2020

Bofill Rdriguez M, Lethaby A, Jordan V. Progestogen-releasing intrauterine systems for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews* 2020, Issue 4. Art. No: CD002126. [DOI: 10.1002/14651858.CD002126.pub3]

Bofill Rodriguez 2021

Bofill Rodriguez M, Lethaby A, Fergusson R. Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews* 2021, Issue 2. Art. No: CD000329. [DOI: 10.1002/14651858.CD000329.pub4]

Bryant-Smith 2018

Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M. Antifibrinolytics for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews* 2018, Issue 4. Art. No: CD000249. [DOI: 10.1002/14651858.CD000249.pub2]

Lethaby 2019

Lethaby A, Wise MR, Weterings MAJ, Bofill Rodriguez M, Brown J. Combined hormonal contraceptives for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews* 2019, Issue 2. Art. No: CD000154. [DOI: 10.1002/14651858.CD000154.pub3]

Marjoribanks 2016

Marjoribanks J, Lethaby A, Farquhar C. Surgery versus medical therapy for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews* 2016, Issue 1. Art. No: CD003855. [DOI: 10.1002/14651858.CD003855.pub3]

References to excluded reviews

Grimes 2006

Grimes DA, Hubacher D, Lopez LM, Schulz KF. Non-steroidal anti-inflammatory drugs for heavy bleeding or pain associated with intrauterine-device use. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No: CD006034. [DOI: 10.1002/14651858.CD006034.pub2]

Gupta 2014

Gupta JK, Sinha A, Lumsden MA, Hickey M. Uterine artery embolization for symptomatic uterine fibroids. *Cochrane Database of Systematic Reviews* 2014, Issue 12. Art. No: CD005073. [DOI: 10.1002/14651858.CD005073.pub4]

Hickey 2012

Hickey M, Higham JM, Fraser I. Progestogens with or without oestrogen for irregular uterine bleeding associated with anovulation. *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No: CD001895. [DOI: 10.1002/14651858.CD001895.pub3]

Liu 2013

Liu JP, Yang H, Xia Y, Cardini F. Herbal preparations for uterine fibroids. *Cochrane Database of Systematic Reviews* 2013, Issue 4. Art. No: CD005292. [DOI: 10.1002/14651858.CD005292.pub3]

Murji 2017

Murji A, Whitaker L, Chow TL, Sobel ML. Selective progesterone receptor modulators (SPRMs) for uterine fibroids. *Cochrane Database of Systematic Reviews* 2017, Issue 4. Art. No: CD010770. [DOI: 10.1002/14651858.CD010770.pub2]

Ping Liu 2013

Liu JP, Yang H, Xia Y, Cardini F. Herbal preparations for uterine fibroids. *Cochrane Database of Systematic Reviews* 2013, Issue 4. Art. No: CD005292. [DOI: 10.1002/14651858.CD005292.pub3]

Ray 2016

Ray S, Ray A. Non-surgical interventions for treating heavy menstrual bleeding (menorrhagia) in women with bleeding disorders. *Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No: CD010338. [DOI: 10.1002/14651858.CD010338.pub3]

Sangkomkamhang 2013

Sangkomkamhang U, Lumbiganon P, Laopaiboon M, Mol BWJ. Progestogens or progestogen-releasing intrauterine systems for uterine fibroids. *Cochrane Database of Systematic Reviews* 2013, Issue 2. Art. No: CD008994. [DOI: 10.1002/14651858.CD008994.pub2]

Song 2013

Song H, Lu D, Navaratnam K, Shi G. Aromatase inhibitors for uterine fibroids. *Cochrane Database of Systematic Reviews* 2013, Issue 10. Art. No: CD009505. [DOI: 10.1002/14651858.CD009505.pub2]

Tan 2013

Tan YH, Lethaby A. Pre-operative endometrial thinning agents before endometrial destruction for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews* 2013, Issue 11. Art. No: CD010241. [DOI: 10.1002/14651858.CD010241.pub2]

Tristan 2012

Tristan M, Orozco LJ, Steed A, Ramírez-Morera A, Stone P. Mifepristone for uterine fibroids. *Cochrane Database of Systematic Reviews* 2012, Issue 8. Art. No: CD007687. [DOI: 10.1002/14651858.CD007687.pub2]

Additional references

(D) Abbott 2003

Abbott J, Hawe J, Hunter D, Garry R. A double-blind randomized trial comparing the Cavaterm and the Novasure endometrial ablation systems for the treatment of dysfunctional uterine bleeding. *Fertility and Sterility* 2003;**80**(1):203-8. [Included in Bofill Rodriguez 2019a]

(D) Agarwal 2016

Agarwal N, Gupta M, Kriplani A, Bhatla N, Singh N. Comparison of combined hormonal vaginal ring with ultralow-dose combined oral contraceptive pills in the management of heavy menstrual bleeding: a pilot study. *Journal of Obstetrics & Gynecology* 2016;**36**:71-5. [Included in Lethaby 2019]

(D) Ashraf 2017

Ashraf MN, Habib-Ur-Rehman A, Shehzad Z, AlSharari SD, Murtaza G. Clinical efficacy of levonorgestrel and norethisterone for the treatment of chronic abnormal uterine bleeding. *Journal of Pakistan Medical Association* 2017;**67**(9):1331-8. [Included in Bofill Rodriguez 2019b and Bofill Rodriguez 2019d] [PMID: 28924270]

(D) Athanatos 2015

Athanatos D, Pados G, Venetis C, Stamatopoulos P, Rousso D, Tsolakidis D, et al. Novasure impedance control system versus microwave endometrial ablation for the treatment of dysfunctional uterine bleeding: a double-blind, randomized controlled trial. *Clinical and Experimental Obstetrics & Gynecology* 2015;**42**(3):347-51. [Included in Bofill Rodriguez 2019a] [PMID: 26152008]

(D) Barrington 2002

Barrington JW, Arunkalaivanan AS, Abdel-Fattah M. Comparison between the levonorgestrel intrauterine system (LNG-IUS) and thermal balloon ablation in the treatment of menorrhagia. *European Journal of Obstetrics and Gynaecology and Reproductive Biology* 2003;**108**:72-4. [Included in Marjoribanks 2016 and Bofill Rodriguez 2019d]

(D) Bhattacharya 1997

Bhattacharya S, Cameron IM, Parkin DE, Abramovich DR, Mollison J, Pinion SB, et al. A pragmatic randomised comparison of transcervical resection of the endometrium with endometrial laser ablation for the treatment of menorrhagia. *British Journal of Obstetrics and Gynaecology* 1997;**104**:601-7. [Included in Bofill Rodriguez 2019a]

(D) Bonduelle 1991

Bonduelle M, Walker JJ, Calder AA. A comparative study of danazol and norethisterone in dysfunctional uterine bleeding presenting as menorrhagia. *Postgraduate Medical Journal* 1991;**67**:833-6. [Included in Bofill Rodriguez 2019b and Beaumont 2007]

(D) Bongers 2004

Bongers MY, Bourdrez P, Mol BWJ, Heintz APM, Brolmann HAM. Randomised controlled trial of bipolar radio-frequency endometrial ablation and balloon endometrial ablation. *British Journal of Obstetrics and Gynaecology* 2004;**111**:1095-102. [Included in Bofill Rodriguez 2019a]

(D) Bonnar 1996

Bonnar J, Sheppard B. Treatment of menorrhagia during menstruation: randomized controlled trial of ethamsylate, mefenamic acid and tranexamic acid. *BMJ* 1996;**313**(7057):579-82. [Included in Bryant-Smith 2018 and Bofill Rodriguez 2019c]

(D) Brun 2006

Brun J-L, Raynal J, Burlet G, Galand B, Quereux C, Bernard P. Cavaterm thermal balloon endometrial ablation versus hysteroscopic endometrial resection to treat menorrhagia: the French, multicenter, randomized study. *Journal of Minimally Invasive Gynecology* 2006;**13**:424-30. [Included in Bofill Rodriguez 2019a]

(D) Buyru 1995

Buyru F, Yalcin O, Kovanci E, Turfanda A. Danazol therapy in dysfunctional uterine bleeding. *Istanbul Tip Fakultesi Mecmuasi* 1995;**58**(3):37-40. [Included in Bofill Rodriguez 2019b and Beaumont 2007]

(D) Callender 1970

Callender ST, Warner GT, Cope E. Treatment of menorrhagia with tranexamic acid. A double blind trial. *British Medical Journal* 1970;**4**(5729):214-6. [Included in Bryant-Smith 2018]

(D) Cameron 1990

Cameron IT, Haining R, Lumsden MA, Thomas VR, Smith SK. The effects of mefenamic acid and norethisterone on measured menstrual blood loss. *Obstetrics and Gynecology* 1990;**76**:85-8. [Included in Bofill Rodriguez 2019b and Bofill Rodriguez 2019c]

(D) Chamberlain

Chamberlain G, Freeman R, Price F, Kennedy A, Green D, Eve L. Raw data from RCT (as supplied prior to 28 April 2022). Lorex Synthélabo Laboratory, UK. [Included in Bofill Rodriguez 2019c]

(D) Clark 2011

Clark TJ, Samuel N, Malick S, Middleton LJ, Daniels J, Gupta JK. Bipolar radiofrequency compared with thermal balloon endometrial ablation in the office. *Obstetrics and Gynecology* 2011;**117**:109-18. [Included in Bofill Rodriguez 2019a]

(D) Cooper 1999

Cooper KG, Bain C, Parkin DE. Comparison of microwave endometrial ablation and transcervical resection of the endometrium for treatment of heavy menstrual loss: a

randomised trial. *Lancet* 1999;**354**:1859-63. [Included in Bofill Rodriguez 2019a]

(D) Cooper 2002

Cooper J, Gimpelson R, Laberge P, Galen D, Garza-Leal JG, Scott J, et al. A randomized, multicenter trial of safety and efficacy of the NovaSure system in the treatment of menorrhagia. *Journal of the American Association of Gynecologic Laparoscopists* 2002;**9**(4):418-28. [Included in Bofill Rodriguez 2019a]

(D) Cooper 2004

Cooper JM, Anderson TL, Fortin CA, Jack SA, Plentl MB. Microwave endometrial ablation vs rollerball electroablation for menorrhagia: a multicenter randomized trial. *Journal of the American Association of Gynecologic Laparoscopists* 2004;**11**(3):394-403. [Included in Bofill Rodriguez 2019a]

(D) Cooper 2019

Cooper K, Breeman S, Scott N, Scotland G, Clark J, et al, on behalf of the HEALTH Study Group. Laparoscopic supracervical hysterectomy versus endometrial ablation for women with heavy menstrual bleeding (HEALTH). *Lancet* 2019;**394**(10207):1425-36. [DOI: http://dx.doi.org/10.1016/S0140-6736(19)31790-8] [Included in Ferguson 2020]

(D) Corson 2000

Corson SL, Brill AI, Brooks PG, Cooper JM, Indman PD, Liu JH, et al. One-year results of the Vesta system for endometrial ablation. *Journal of the American Association of Gynecologic Laparoscopists* 2000;**7**(4):489-97. [Included in Bofill Rodriguez 2019a]

(D) Corson 2001

Corson SL. A multicenter evaluation of endometrial ablation by hydrothermablator and rollerball for treatment of menorrhagia. *Journal of the American Association of Gynecologic Laparoscopists* 2001;**8**(3):359-67. [Included in Bofill Rodriguez 2019a]

(D) Crosignani 1997

Crosignani PG, Vercellini P, Apolone G, De Giorgi O, Cortesi I, Meschia M. Endometrial resection versus vaginal hysterectomy for menorrhagia: long-term clinical and quality-of-life outcomes. *American Journal of Obstetrics and Gynecology* 1997;**177**(1):95-101. [Included in Ferguson 2020]

(D) Crosignani 1997a

Crosignani PG, Vercellini P, Mosconi P, Oldani S, Cortesi I, de Giorgi O. Levonorgestrel-releasing intrauterine device versus hysteroscopic endometrial resection in the treatment of dysfunctional uterine bleeding. *Obstetrics and Gynecology* 1997;**90**:257-63. [CRSREF 286340] [Included in Marjoribanks 2016 and Included in Bofill Rodriguez 2019d]

(D) Dahiya 2016

Dahiya P, Dalal M, Yadav A, Dahiya K, Jain S, Silan V. Efficacy of combined hormonal vaginal ring in comparison to combined hormonal pills in heavy menstrual bleeding. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2016;**203**:147-51. [DOI: 10.1016/j.ejogrb.2016.05.009] [Included in Lethaby 2019]

(D) De Souza 2010

De Souza SS, Camargos AF, de Rezende CP, Pereira FA, Araujo CA, Silva Filho AL. A randomized prospective trial comparing the levonorgestrel-releasing intrauterine system with thermal balloon ablation for the treatment of heavy menstrual bleeding [Contraception]. *2010* 81;**3**:226-31. [CRSREF 286343] [Included in Marjoribanks 2016 and Bofill Rodriguez 2019d]

(D) Dickersin 2007

Dickersin K, Munro MG, Clark M, Langenberg P, Scherer R, Frick K, et al. Hysterectomy compared with endometrial ablation for dysfunctional uterine bleeding. *Obstetrics and Gynecology* 2007;**110**(6):1279-89. [Included in Ferguson 2020]

(D) Dockeray 1989

Dockeray CJ, Sheppard BL, Bonnar J. Comparison between mefenamic acid and danazol in the treatment of established menorrhagia. *British Journal of Obstetrics and Gynaecology* 1989;**96**:840-4. [Included in Beaumont 2007]

(D) Duleba 2003

Duleba AJ, Heppard MC, Soderstrom RM, Townsend DE. A randomized study comparing endometrial cryoablation and rollerball electroablation for treatment of dysfunctional uterine bleeding. *Journal of the American Association of Gynecologic Laparoscopists* 2003;**10**(1):17-26. [Included in Bofill Rodriguez 2019a]

(D) Dunphy 1998

Dunphy BC, Goerzen J, Greene CA, De La Ronde S, Seidel J, Ingelson B. A double blind randomised study comparing danazol and medroxyprogesterone acetate in the management of menorrhagia. *Journal of Obstetrics and Gynaecology* 1998;**18**(6):553-5. [Included in Beaumont 2007]

(D) Dwyer 1993

Dwyer N, Hutton J, Stirrat GM. Randomised controlled trial comparing endometrial resection with abdominal hysterectomy for the surgical treatment of menorrhagia. *British Journal of Obstetrics and Gynaecology* 1993;**100**(3):237-43. [Included in Ferguson 2020]

(D) Edlund 1995

Edlund M, Andersson K, Rybo G, Lindoff CC, Astedt B, Schoult BV. Reduction of menstrual blood loss in women suffering from idiopathic menorrhagia with a novel antifibrinolytic drug (Kabi2161). *British Journal of Obstetrics and Gynaecology* 1995;**102**(11):913-7. [Included in Bryant-Smith 2018]

(D) Endrikat 2009

Endrikat J, Shapiro H, Lukkari-Lax E, Kunz M, Schmidt W, Fortier M. A Canadian, multicentre study comparing efficacy of a levonorgestrel-releasing intrauterine system to an oral contraceptive in women with idiopathic menorrhagia. *Journal of Obstetrics and Gynaecology Canada* 2009;**31**(4):340-7. [Included in Lethaby 2019 and Bofill Rodriguez 2019d]

(D) Ergun 2012

Ergun B, Kuru O, Sen S, Kilic Y, Bastu E. Roller-ball endometrial ablation versus levonorgestrel releasing intrauterine system in the management of abnormal uterine bleeding. *Gineco.eu* 2012;**8**(4):199-201. [CRSREF 286346] [Included in Marjoribanks 2016 and Bofill Rodriguez 2019d]

(D) Fraser 1981

Fraser IS, Pearse C, Shearman RP, Elliott PM, McIlveen J, Markham R. Efficacy of mefenamic acid in patients with a complaint of menorrhagia. *Obstetrics & Gynaecology* 1981;**58**(5):543-51. [Included in Bofill Rodriguez 2019c]

(D) Fraser 1991

Fraser IS, McCarron G. Randomized trial of 2 hormonal and 2 prostaglandin-inhibiting agents in women with a complaint of menorrhagia. *Australian & New Zealand Journal of Obstetrics & Gynaecology* 1991;**31**:66-70. [Included in Lethaby 2019, Bofill Rodriguez 2019c and Beaumont 2007]

(D) Fraser 2011

Fraser IS, Romer T, Parke S, Zeun S, Mellinger U, Machlitt A, Jet al. Effective treatment of heavy and/or prolonged menstrual bleeding with an oral contraceptive containing estradiol valerate and dienogest: a randomized double-blind Phase III trial. *Human Reproduction* 2011;**26**(10):2698-708. [DOI: 10.1093/humrep/der224] [Included in Lethaby 2019]

(D) Freeman 2011

Freeman EW, Lukes A, VanDrie D, Mabey RG, Gersten J, Adomako TL. A dose-response study of a novel, oral tranexamic formulation for heavy menstrual bleeding. *American Journal of Obstetrics and Gynecology* 2011;**205**(4):319.e1-319.e7. [Included in Bryant-Smith 2018]

(D) Gannon 1991

Gannon MJ, Holt EM, Fairbank J, Fitzgerald M, Milne MA, Crystal AM, et al. A randomised trial comparing endometrial resection and abdominal hysterectomy for the treatment of menorrhagia. *BMJ (Clinical Research Ed.)* 1991;**303**(6814):1362-4. [Included in Ferguson 2020]

(D) Ghazizadeh 2014

Ghazizadeh S, Panahi Z, Ghanbari Z, Menshadi AT, Farahmandian T, Javadian P. Comparative efficacy of NovaSure, the levonorgestrel-releasing intrauterine system, and hysteroscopic endometrial resection in the treatment of menorrhagia: a randomized clinical trial. *Journal of Gynecologic Surgery* 2014;**30**(4):215-8. [Data reported in a way that do not allowed comparisons] [Included in Marjoribanks 2016, Bofill Rodriguez 2019a and Bofill Rodriguez 2019d]

(D) Goshtasebi 2013

Goshtasebi A, Moukhah S, Gandevani SB. Treatment of heavy menstrual bleeding of endometrial origin: randomized controlled trial of medroxyprogesterone acetate and tranexamic acid. *Archives of Gynecology and Obstetrics* 2013;**288**(5):1055-60. [Included in Bryant-Smith 2018 and Bofill Rodriguez 2019b]

(D) Grover 1990

Grover V, Usha R, Gupta U, Kalra S. Management of cyclical menorrhagia with prostaglandin synthetase inhibitor. *Asia-Oceania Journal of Obstetrics & Gynaecology* 1990;**16**:255-9. [Included in Bofill Rodriguez 2019c]

(D) Hashim 2012

Hashim HA, Alsherbini W, Bazeed M. Contraceptive vaginal ring treatment of heavy menstrual bleeding: a randomized controlled trial with norethisterone. *Contraception* 2012;**85**:246-52. [Included in Lethaby 2019 and Bofill Rodriguez 2019b]

(D) Hawe 2003

Hawe J, Abbott J, Hunter D, Phillips G, Garry R. A randomised controlled trial comparing the Cavaterm endometrial ablation system with the Nd:YAG laser for the treatment of dysfunctional uterine bleeding. *British Journal of Obstetrics and Gynaecology* 2003;**110**:350-7. [Included in Bofill Rodriguez 2019a]

(D) Herman 2013

Beelen P, Van Den Brink MJ, Geomini P, Dekker J, Herman M, Duijnhoven R, Mol B, Berger M, Bongers M. RCT comparing the LNG-IUS versus endometrial ablation in women with heavy menstrual bleeding (MIRA). *International Journal of Gynecology and Obstetrics* 2018;**143**(3):318-319. [10.1002/ijgo.12582] [Included in Bofill Rodriguez 2019d]

(D) Higham 1993

Higham JM, Shaw RW. A comparative study of danazol, a regimen of decreasing doses of danazol, and norethindrone in the treatment of objectively proven unexplained menorrhagia. *American Journal of Obstetrics and Gynecology* 1993;**169**:1134-9. [Included in Bofill Rodriguez 2019b and Beaumont 2007]

(D) Hurskainen 2004

Hurskainen R, Teperi J, Rissanen P, Aalto AM, Grenman S, Kivela A, et al. Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for the treatment of menorrhagia. *JAMA* 2004;**291**(12):1456-63. [Included in Marjoribanks 2016 and Bofill Rodriguez 2019d]

(D) Irvine 1988

Irvine GA, Campbell-Brown MB, Lumsden MA, Heikkila A, Walker JJ, Cameron IT. Randomised comparative trial of the levonorgestrel intrauterine system and norethisterone for treatment of idiopathic menorrhagia. *British Journal of Obstetrics and Gynaecology* 1988;**105**(6):592-8. [Included in Bofill Rodriguez 2019b]

(D) Istre 1998

Rauramo I, Elo I, Istre O. Long-term treatment of menorrhagia with levonorgestrel intrauterine system versus endometrial resection. *Obstetrics and Gynecology* 2004;**104**(6):1314-21. [Included in Marjoribanks 2016]

(D) Jain 2016

Jain P, Rajaram S, Gupta B, Goel N, Srivastava H. Randomized controlled trial of thermal balloon ablation versus vaginal hysterectomy for leiomyoma-induced heavy menstrual bleeding. *International Journal of Gynaecology and Obstetrics*

2016;**135**(2):140-4. [Included in Ferguson 2020] [https://doi.org/10.1016/j.ijgo.2016.04.020]

(D) Jaisamrarn 2006

Jaisamrarn U, Sitavarin S, Suwikrom S, Kamolpornwijit W. Randomized trial of medical therapies for menorrhagia: clinical efficacy and effect on quality of life. In: XVIII FIGO World Congress of Gynecology and Obstetrics; 2006 Nov 5-10; Kuala Lumpur (Malaysia). Vol. 3. 2006:83. [Included in Bryant-Smith 2018 and Bofill Rodriguez 2019c]

(D) Jensen 2011

Jensen JT, Parke S, Mellinger U, Machlitt A, Fraser IS. Effective treatment of heavy menstrual bleeding with estradiol valerate and dienogest. *Obstetrics & Gynecology* 2011;**117**:777-87. [DOI: 10.1097/AOG.Ob013e3182118ac3] [Included in Lethaby 2019]

(D) Kaunitz 2010

Kaunitz AM, Bissonnette F, Monteiro I, Lukkari-Lax E, Muysers C, Jensen JT. Levonorgestrel-releasing intrauterine system or medroxyprogesterone for heavy menstrual bleeding. *Obstetrics and Gynecology* 2010;**116**:3625-32. [CRSREF: 328939] [Included in Bofill Rodriguez 2019b and Bofill Rodriguez 2019d]

(D) Kiseli 2016

Kiseli M, Kayikcioglu F, Evliyaoglu O, Haberal A. Comparison of therapeutic efficacies of norethisterone, tranexamic acid and levonogestrel-releasing intrauterine system for the treatment of heavy menstrual bleeding: a randomized controlled study. *Gynecologic and Obstetric Investigation* 2016;**81**(5):447-53. [Included in Bryant-Smith 2018, Bofill Rodriguez 2019b and Bofill Rodriguez 2019d]

(D) Kittelsen 1998

Kittelsen N, Istre O. A randomized study comparing levonorgestrel intrauterine system (LNG IUS) and transcervical resection of the endometrium (TCRE) in the treatment of menorrhagia: preliminary results. *Gynecological Endocrinology* 1998;**7**:61-5. [Included in Bofill Rodriguez 2019d]

(D) Kriplani 2006

Kriplani A, Kulshrestha V, Agarwal N, Diwakar S. Role of tranexamic acid in management of dysfunctional uterine bleeding in comparison with medroxyprogesterone acetate. *Journal of Obstetrics and Gynaecology* 2006;**26**(7):673-8. [Included in Bryant-Smith 2018 and Bofill Rodriguez 2019b]

(D) Laberge 2017

Laberge P, Garza-Leal J, Fortin C, Grainger D, Johns DA, Adkins RT, et al. A randomized controlled multicenter US Food and Drug Administration trial of the safety and efficacy of the Minerva Endometrial Ablation System: one-year follow-up results. *Journal of Minimally Invasive Gynecology* 2017;**24**(1):124-32. [DOI: 10.1016/j.jmig.2016.09.009] [Included in Bofill Rodriguez 2019a]

(D) Lukes 2010

Lukes AS, Moore KA, Muse KN, Gersten JK, Hecht BR, Edlund M, et al. Tranexamic acid treatment for heavy menstrual bleeding. *Obstetrics and Gynecology* 2010;**116**(4):865-75. [Included in Bryant-Smith 2018]

(D) Malak 2006

Malak KA, Shawki O. Management of menorrhagia with the levonorgestrel intrauterine system versus endometrial resection. *Gynecological Surgery* 2006;**3**:275-80. [Included in Marjoribanks 2016 and Bofill Rodriguez 2019d]

(D) McClure 1992

McClure N, Marners M, Healy DL, Hill DJ, Lawrence AS, Wingfield M, et al. A quantitative assessment of endometrial electrocautery in the management of menorrhagia and a comparative report of argon laser endometrial ablation. *Gynaecological Endoscopy* 1992;**1**:199-202. [Included in Bofill Rodriguez 2019a]

(D) Meyer 1998

Meyer WR, Walsh BW, Grainger DA, Peacock LM, Loffer FD, Steege JF. Thermal balloon and rollerball ablation to treat menorrhagia: a multicenter comparison. *Obstetrics and Gynecology* 1998;**92**:98-103. [Included in Bofill Rodriguez 2019a]

(D) Muggeridge 1983

Muggeridge J, Elder MG. Mefenamic acid in the treatment of menorrhagia. *Research and Clinical Forums* 1983;**5**:83-8. [Included in Bofill Rodriguez 2019c]

(D) O'Connor 1997

O'Connor H, Broadbent JA, Magos AL, McPherson K. Medical Research Council randomised trial of endometrial resection versus hysterectomy in management of menorrhagia. *Lancet* 1997;**349**(9056):897-901. [Included in Ferguson 2020]

(D) Ozdegirmenci 2011

Ozdegirmenci O, Kayikcioglu F, Akgul MA, Kaplan M, Karcaaltincaba M, Haberal A, et al. Comparison of levonorgestrel intrauterine system versus hysterectomy on efficacy and quality of life in patients with adenomyosis. *Fertility and Sterility* 2011;**95**(2):497-502. [Included in Bofill Rodriguez 2019d]

(D) Pellicano 2002

Pellicano M, Guida M, Acunzo G, Cirillo D, Bifulco G, Nappi C. Hysteroscopic transcervical endometrial resection versus thermal destruction for menorrhagia: a prospective randomized trial on satisfaction rate. *American Journal of Obstetrics and Gynecology* 2002;**187**:545-50. [Included in Bofill Rodriguez 2019a]

(D) Penninx 2010

Penninx JPM, Mol BW, Engels R, van Rumste MME, Kleijn C, Koks CAM, et al. Bipolar radiofrequency endometrial ablation compared with hydrothermablation for dysfunctional uterine bleeding. *Obstetrics and Gynecology* 2010;**116**:819-26. [Included in Bofill Rodriguez 2019a]

(D) Penninx 2016

Penninx J, Herman M, Kruitwagen R, Ter Haar A, Mol B, Bongers M. Bipolar versus balloon endometrial ablation in the office: a randomized controlled trial. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2016;**196**:52-6. [DOI: 10.1016/j.ejogrb.2015.10.010] [Included in Bofill Rodriguez 2019a]

(D) Perino 2004

Perino A, Castelli A, Cucinella G, Biondo A, Pane A, Venezia R. A randomized comparison of endometrial laser intrauterine thermotherapy and hysteroscopic endometrial resection. *Fertility and Sterility* 2004;**82**:731-4. [Included in Bofill Rodriguez 2019a]

(D) Pinion 1994

Pinion SB, Parkin DE, Abramovich DR, Naji A, Alexander DA, Russell IT, et al. Randomised trial of hysterectomy, endometrial laser ablation, and transcervical endometrial resection for dysfunctional uterine bleeding. *British Medical Journal (Clinical Research Ed.)* 1994;**309**(6960):979-83. [Included in Ferguson 2020]

(D) Preston 1995

Preston JT, Cameron IT, Adams EJ, Smith SK. Comparative study of tranexamic acid and norethisterone in the treatment of ovulatory menorrhagia. *British Journal of Obstetrics and Gynaecology* 1995;**102**(5):401-6. [Included in Bryant-Smith 2018 and Bofill Rodriguez 2019b]

(D) Romer 1998

Romer T. The treatment of recurrent menorrhagias - Cavaterm-balloon-coagulation versus Rollerball-endometrial ablation - a prospective randomized comparative study [Die therapie rezidivierender Menorrhagien - Cavaterm-Ballon-Koagulatioon versus Roller-Ball-Endometriumkoagulation - eine prospektive randomisierte Vergleichsstudie]. *Zentralblatt fur Gynakologie* 1998;**120**(10):511-4. [Included in Bofill Rodriguez 2019a]

(D) Sambrook 2009

Sambrook AM, Cooper KG, Campbell MK, Cook JA. Clinical outcomes from a randomised comparison of microwave endometrial ablation with thermal balloon endometrial ablation for the treatment of heavy menstrual bleeding. *British Journal of Obstetrics and Gynaecology* 2009;**116**:1038-45. [Included in Bofill Rodriguez 2019a]

(D) Sayed 2011

Sayed GH, Zakherah MS, El-Nashar SA, Shaaban MM. A randomised clinical trial of a levonorgestrel-releasing intrauterine system and a low-dose combined oral contraceptive for fibroid-related menorrhagia. *International Journal of Gynecology and Obstetrics* 2011;**112**:126-30. [Included in Bofill Rodriguez 2019d]

(D) Sesti 2011

Sesti F, Ruggeri V, Pietropolli A, Piancatelli R, Piccione E. Thermal balloon ablation versus laparoscopic supracervical hysterectomy for the surgical treatment of heavy menstrual bleeding: a randomized study. *Journal of Obstetrics and Gynaecology Research* 2011;**37**(11):1650-7. [Included in Ferguson 2020]

(D) Sesti 2012

Sesti F, Piancatelli R, Pietropolli A, Ruggeri V, Piccione E. Levonorgestrel-releasing intrauterine system versus laparoscopic supracervical hysterectomy for the treatment of heavy menstrual bleeding: a randomized study. *Journal of Women's Health* 2012;**21**(8):851-7. [Included in Marjoribanks 2016 and Included in Bofill Rodriguez 2019d]

(D) Shabaan 2011

Shabaan MM, Zakherah MS, El-Nashar SA, Sayed GH. Levonorgestrel-releasing intrauterine system compared to low dose combined oral contraceptive pills for idiopathic menorrhagia: a randomized clinical trial. *Contraception* 2011;**83**:48-54. [DOI: 10.1016/j.contraception.2010.06.011] [Included in Lethaby 2019 and Included in Bofill Rodriguez 2019d]

(D) Shaw 2007

Shaw R, Symonds IM, Tamizian O, Chaplain J, Mukhopadhyay S. Randomised comparison of thermal balloon ablation and levonorgestrel intrauterine system in patients with idiopathic menorrhagia. *Australian and New Zealand Journal of Obstetric and Gynaecology* 2007;**47**:335-40. [Included in Marjoribanks 2016 and Bofill Rodriguez 2019d]

(D) Soysal 2002

Soysal M, Soysal S, Ozer S. A randomized controlled trial of levonorgestrel releasing IUD and thermal balloon ablation in the treatment of menorrhagia. *Zentralblatt fur Gynakologie* 2002;**124**(4):213-9. [Included in Marjoribanks 2016 Bofill Rodriguez 2019d]

(D) Talis 2006

Busfield RA, Farquhar CM, Sowter MC, Lethaby A, Sprecher M, Yu Y, et al. A randomised trial comparing the levonorgestrel intrauterine system and thermal balloon ablation for heavy menstrual bleeding. *BJOG: an International Journal of Obstetrics and Gynaecology* 2006;**113**:257-63. [Included in Marjoribanks 2016 and Bofill Rodriguez 2019d]

(D) Tam 2006

Tam WH, Yuen PM, Ng DPS, Lung PL, Lok IH, Rogers MS. Health status function after treatment with thermal balloon endometrial ablation and levonorgestrel intrauterine system for idiopathic menorrhagia: a randomised study. *Gynecologic and Obstetric Investigation* 2006;**62**:84-8. [Included in Marjoribanks 2016 Bofill Rodriguez 2019d]

(D) Tsang 1987

Tsang BK, Domingo MT, Spence JE, Garner PR, Dudley DK, Oxorn H. Endometrial prostaglandins and menorrhagia: influence of a prostaglandin synthetase inhibitor *in vivo*. *Canadian Journal of Physiology and Pharmacology* 1987;**65**:2081-4. [Included in Bofill Rodriguez 2019c]

(D) van Eijkeren 1992

van Eijkeren MA, Christiaens GC, Geuze HJ, Haspels AA, Sixma JJ. Effects of mefenamic acid on menstrual hemostasis in essential menorrhagia. *American Journal of Obstetrics and Gynecology* 1992;**166**:1419-28. [Included in Bofill Rodriguez 2019c]

(D) van Zon-Rabelink 2003

van Zon-Rabelink IAA, Vleugels MPH, Merkus HMWM, de Graaf R. Endometrial ablation by rollerball electrocoagulation compared to uterine balloon thermal ablation. Technical and safety

aspects. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2003;**110**:220-3. [Included in Bofill Rodriguez 2019a]

(D) Vercellini 1999

Vercellini P, Oldani S, Yaylayan L, Zaina B, De Giorgi O, Crosignani PG. Randomised comparison of vaporising electrode and cutting loop for endometrial ablation. *Obstetrics and Gynecology* 1999;**94**:521-7. [Included in Bofill Rodriguez 2019a]

(D) Ylikorkala 1986

Ylikorkala O, Pekonen F. Naproxen reduces idiopathic but not fibromyoma-induced menorrhagia. *Obstetrics & Gynaecology* 1986;**68**:10-2. [Included in Bofill Rodriguez 2019c]

(D) Zhang 2008

Zhang Y, He F, Sun Z, LI S, Bi S, Huang X, et al. A multicenter, prospective, randomized, open comparator study on the treatment of ovulatory menorrhagia with tranexamic acid and norethisterone in China. *Chinese Journal of Obstetrics and Gynaecology* 2008;**43**(4):247-50. [Included in Bryant-Smith 2018 and Bofill Rodriguez 2019b]

(D) Zupi 2003

Zupi E, Zullo F, Marconi D, Sbracia M, Pellicano M, Solima E, et al. Hysteroscopic endometrial resection versus laparoscopic supracervical hysterectomy for menorrhagia: a prospective randomised trial. *American Journal of Obstetrics and Gynecology* 2003;**188**(1):7-12. [Included in Ferguson 2020]

(N) Andersch 1988

Andersch B, Milsom I, Rybo G. An objective evaluation of flurbiprofen and tranexamic acid in the treatment of idiopathic menorrhagia. *Acta Obstetricia et Gynecologica Scandinavica* 1988;**67**:645-8. [Data reported in a way that do not allow comparisons] [Included in Bofill Rodriguez 2019c]

(N) Boujida 2002

Boujida VH, Philipsen T, Pelle J, Joergensen JC. Five-year follow-up of endometrial ablation: endometrial coagulation versus endometrial resection. *Obstetrics and Gynecology* 2002;**99**:988-92. [Included in Bofill Rodriguez 2019a]

(N) Cameron 1987

Cameron IT, Leask R, Kelly RW, Baird DT. The effects of danazol, mefenamic acid, norethisterone and a progesterone-impregnated coil on endometrial prostaglandin concentrations in women with menorrhagia. *Prostaglandins* 1987;**34**:99-110. [Included in Bofill Rodriguez 2019b, Bofill Rodriguez 2019c and Beaumont 2007]

(N) Chimbira 1980

Chimbira T, Andreson A, Naish C, Cope E, Turnbull A. Reduction of menstrual blood loss by danazol in unexplained menorrhagia: lack of effect of placebo. *British Journal of Obstetrics and Gynaecology* 1980;**87**(12):1152-8. [Excluded as is a comparison between different dosages of danazol] [Included in Beaumont 2007] [PMID: 7002206]

(N) Cooper 1997

Cooper KG, Parkin DE, Garratt AM, Grant AM. A randomised comparison of medical and hysteroscopic management in women consulting a gynaecologist for treatment of heavy menstrual loss. *British Journal of Obstetrics and Gynaecology* 1997;**104**:1360-6. [CRSREF 2868337] [Included in Marjoribanks 2016] [No randomization on the medical treatment arm]

(N) Fathima 2012

Fathima A, Sultana A. Clinical efficacy of a Unani formulation 'Safoof Habis' in menorrhagia: a randomized controlled trial. *European Journal of Integrative Medicine* 2012;**4**(3):e315-22. [Excluded as comparison is not medical treatment] [Included in Bryant-Smith 2018]

(N) Goshtasebi 2015

Goshtasebi A, Mazari Z, Behboudi Gandevani S, Naseri M. Anti-hemorrhagic activity of Punica granatum L. flower (Persian Golnar) against heavy menstrual bleeding of endometrial origin: a double-blind, radomized controlled trial. *Medical Journal of the Islamic Republic of Iran* 2015;**29**:199. [Comparison was not a medical treatment] [Included in Bryant-Smith 2018]

(N) Gupta 2013

Gupta J, Kai J, Middleton L, Pattison H, Gray R, Daniels J. Levonorgestrel intrauterine system versus medical therapy for menorrhagia. *New England Journal of Medicine* 2013;**368**:128-37. [Included in Bofill Rodriguez 2019d] [one arm was not randomized]

(N) Hall 1987

Hall P, MacLachlan N, Thorn N, Nudd MW, Taylor CG, Garrioch DB. Control of menorrhagia by the cyclo-oxygenase inhibitors naproxen sodium and mefenamic acid. *British Journal of Obstetrics and Gynaecology* 1987;**94**:554-8. [Included in Bofill Rodriguez 2019c]

(N) Khajehei 2013

Khajehei N, Abdali K, Tabatabaee. The effect of mefenamic acid and naproxen on heavy menstrual bleeding: A placebo-controlled study. *South African Journal of Obstetricsand gynaecology* 2013;**19**(2):31-34. [DOI: 10.7196/SAJOG.587]

(N) Kilic 2009

Kilic S, Yuksel B, Doganay M, Bardakci H, Akinsu F, Uzunlar O, et al. The effect of levonorgestrel-releasing intrauterine device on menorrhagia in women taking anticoagulant medication after cardiac valve replacement. *Contraception* 2009;**80**(2):152-7. [Included in Bofill Rodriguez 2019d]

(N) Kupperman 2004

Kupperman M, Varner RE, Summitt RL, Learman LA, Ireland C, Vittinghoff E, et al. Effect of hysterectomy vs medical treatment on health-related quality of life and sexual functioning. *JAMA* 2004;**291**(12):1447-55. [Included in Marjoribanks 2016] [No randomization on the medical treatment arm]

(N) Lamb 1987

Lamb MP. Danazol in menorrhagia: a double blind placebo controlled trial. *Journal of Obstetrics and Gynaecology*

1987;**7**:212-16. [Compares Danazol and placebo] [Included in Beaumont 2007]

(N) Makarainen 1986

Makarainen L, Ylikorkala O. Primary and myoma-associated menorrhagia: role of prostaglandin and effects of ibuprofen. *British Journal of Obstetrics and Gynaecology* 1986;**93**:974-8. [Included in Bofill Rodriguez 2019c]

(N) Najam 2010

Najam R, Agarwald D, Tyagi R, Singh S. Comparison of tranexamic acid with a combination of tranexamic acid and mefenamic acid in reducing menstrual blood loss in ovulatory dysfunctional uterine bleeding. *Journal of Clinical and Diagnostic Research* 2010;**4**:3020-5. [Included in Bofill Rodriguez 2019c] [No data available for the comparisons]

(N) Onoglu 2007

Onoglu A, Taskin O, Inal M, Sadik S, Simsek M, Akar M, et al. Comparison of the long-term histopathologic and morphologic changes after endometrial rollerball ablation and resection: a prospective randomized trial. *Journal of Minimally Invasive Gynecology* 2007;**14**:39-42. [(E) The only review outcome reported was surgical time] [Included in Bofill Rodriguez 2019a]

(N) Reid 2005

Reid PC, Virtanen-Kari S. Randomised comparative trial of the levonorgestrel intrauterine system and mefenamic acid for the treatment of idiopathic menorrhagia: a multiple analysis using total menstrual fluid loss, menstrual blood loss and pictorial blood loss assessment charts. *British Journal of Obstetrics and Gynaecology* 2005;**112**:1121-5. [Data reported in ranges] [Included in Bofill Rodriguez 2019c and Bofill Rodriguez 2019d]

(N) Shravage 2011

Shravage J, Mekhala D, Bellad MB, Ganachari MS, Dhumale HA. Ormeloxifene versus medroxyprogesterone acetate (MPA) in the treatment of dysfunctional uterine bleeding. A double blind randomized controlled trial. *Journal of South Asian Federation of Obstetrics and Gynaecology* 2011;**3**(1):21-4. [10.5005/jp-journals-10006-1116] [Data was reported in a format that do not allow comparisons] [Included in Bofill Rodriguez 2019b]

(N) Thabet 2010

Thabet SMA. New attempt using ablative curettage technique for managing benign premenopausal uterine bleeding. *Obstetrics and Gynaecology Research* 2010;**36**(4):803-9. [Included in Bofill Rodriguez 2019a] [No data for comaprisons (overcouretage)]

Alvarado 2001

Alvarado RG, Liu JY, Zwolak RM. Danazol and limb-threatening arterial thrombosis: two case reports. *Journal of Vascular Surgery* 2001;**34**(6):1123-6. [DOI: 10.1067/mva.2001.118078]

Alvaro 1996

Alvaro D, Piat C, Francia C, Franchitto A, Furfaro S, Valente C et al. Ultrastructural features of danazol-induced cholestasis: a case study. *Ultrastructural Pathology* 1996;**20**(5):491-5. [DOI: 10.3109/01913129609016353]

Audia 2016

Audia S, Godeau B, Bonnotte B. Is there still a place for "old therapies" in the management of immune thrombocytopenia? *La Revue de Medecine Interne* 2016;**37**(1):43-9. [DOI: 10.1016/j.revmed.2015.08.007]

Bacchi 2012

Bacchi S, Palumbo P, Sponta A, Coppolino M. Clinical pharmacology of non-steroidal anti-inflammatory drugs: a review. *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry* 2012;**11**(1):52-64. [DOI: 10.2174/187152312803476255]

Blacker 1902

Blacker JF. Vaporization of the uterus. *British Journal of Obstetrics and Gynaecologu: An International Journal of Obstetrics & Gynaecology* 1902;**1**(5):488-511.

Bofill Rodriguez 2020a

Bofill Rodriguez M, Lethaby A, Farquhar C, Duffy JM. Interventions commonly available during pandemics for heavy menstrual bleeding: an overview of Cochrane Reviews.. *Cochrane Database of Systematic Reviews* 2020, Issue 7. Art. No: CD013651. [DOI: 10.1002/14651858.CD013651.pub2]

Bongers 2004

Bongers MY, Mol BW, Brölmann HA. Current treatment of dysfunctional uterine bleeding. *Maturitas* 2004;**47**(3):159-74. [DOI: 10.1016/j.maturitas.2003.08.002. PMID: 15036486]

Bradley 2016

Bradley L, Guyen N. The medical management of abnormal uterine bleeding in reproductive-aged women. *American Journal of Obstetrics and Gynecology* 2015;**214**(1):31-44. [DOI: 10.1016/j.ajog.2015.07.044]

Brignardello-Petersen2017

Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, et al. GRADE Working Group. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis.. *Journal of Clinical Epidemiology* 2018;**93**:36-44. [DOI: 10.1016/j.jclinepi.2017.10.005] [Erratum in: J Clin Epidemiol. 2018 Jun;98:162. PMID: 29051107.]

Brignardello-Petersen 2019

Brignardello-Petersen R, Mustafa RA, Siemieniuk RAC, Murad MH, Agoritsas T, Izcovich A et al, GRADE Working Group. GRADE approach to rate the certainty from a network meta-analysis: addressing incoherence. *Journal of Clinical Epidemiology* 2019;**108**:77-85. [DOI: 10.1016/j.jclinepi.2018.11.025]

Brignardello-Petersen 2020

Brignardello-Petersen R, Izcovich, A, Rochwerg B, Florez I, Hazlewood G, et al. GRADE approach to drawing conclusions from a network meta-analysis using a partially contextualised framework. *BMJ* 2020;**371**:m3907. [DOI: 10.1136/bmj.m3907]

Brunskill 1992

Brunskill P. The effects of fetal exposure to danazol. *British Journal of Obstetetrics and Gynaecology* 1992;**99**(3):212-5. [PMID: 1606119]

Caldwell 2014

Caldwell DM. An overview of conducting systematic reviews with network meta-analysis. *Systematic Reviews Journal* 2014;**3**:109. [DOI: 10.1186/2046-4053-3-109]

Clarke-Pearson 2013

Clarke-Pearson D, Geller E. Complications of hysterectomy. *Obstetrics & Gynecology* 2013;**121**(3):654-73. [DOI: 10.1097/AOG.0b013e3182841594]

Cole 1971

Cole S, Billewicz W, Thomson A. Sources of variation in menstrual blood loss. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1971;**78**:933-9. [PMID: 5111902]

COMET 2018

Cooper N, Khan K, Rivas C. Defining core outcomes for clinical trials of heavy menstrual bleeding. A Core Outcome sets for Gynaecological conditions (COGS) project. www.comet-initiative.org/studies/details/789 (accessed prior to 28 April 2022).

Coulter 1995

Coulter A, Kelland J, Peto V, Rees M. Treating menorrhagia in primary care. An overview of drug trials and a survey of prescribing practice. *International Journal of Technology Assessment in Health Care* 1995;**11**(3):456-71. [PMID: 7591547]

Daniels 2012

Daniels J, Middleton L, Champaneria R, Khan K, Cooper K, Bhattacharya S, et al. Second generation endometrial ablation techniques for heavy menstrual bleeding: network meta-analysis. *BMJ* 2012;**344**:e2564. [DOI: https://doi.org/10.1136/bmj.e2564]

De Bastos 2014

De Bastos M, Stegeman BH, Rosendaal FR, Van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, et al. Combined oral contraceptives: venous thrombosis. *Cochrane Database of Systematic Reviews* 2014, Issue 3. Art. No: CD010813. [DOI: 10.1002/14651858.CD010813.pub2]

Dias 2010

Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine* 2010;**28**(7-8):932-44. [DOI: 10.1002/sim.3767]

Dias 2018

Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ. Network Meta-analysis for Decision Making. Wiley, 2018. [DOI: 10.1002/9781118951651] [Online ISBN:9781118951651]

Dias 2019

Dias S, Caldwell D. Network meta-analysis explained. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2019;**104**(1):F8-F12. [DOI: 10.1136/archdischild-2018-315224]

Di Carlo, 2015

Di Carlo C, Guida M, De Rosa N, Sansone A, Gargano V, Cagnacci A, et al. Bleeding profile in users of an etonogestrel sub-dermal implant: effects of anthropometric variables. An observational uncontrolled preliminary study in Italian population. *Gynaecological Endocrinology* 2015;**31**(6):491-4. [DOI: 10.3109/09513590.2015.1018163]

Edlund 2011

Edlund M. Nonhormonal treatments for heavy menstrual bleeding. *Journal of Women's Health* 2011;**20**(11):1645-53. [DOI: 10.1089/jwh.2010.2696]

Famuyide 2018

Famuyide A. Endometrial Ablation. *Journal of Minimally Invasive Gynecoly* 2018;**25**(2):299-307. [DOI: 10.1016/j.jmig.2017.08.656]

Fraser 2009

Fraser I, Langham S, Uhl-Hochgraeber K. Health-related quality of life and economic burden of abnormal uterine bleeding. *Expert Review of Obstetrics & Gynecology* 2009;**4**(2):179-89. [DOI: 10.1586/17474108.4.2.179]

Friberg 2006

Friberg B, Orno A, Lindgren A, Lethagen S. Bleeding disorders among young women: a population-based prevalence study. *Acta Obstetetrica et Gynecologica Scandinavica* 2006;**85**(2):200-6. [DOI: 16532915]

Fritz 2012

Fritz M, Speroff L. Clinical Gynecologic Endocrinology and Infertility. Wolters Kluwer Health/Lippincott Williams & Wilkins, 2012. [https://slycksyxr01.storage.googleapis.com/MDc4MTc3OTY4NQ==01.pdf]

Garay 2006

Garay RP, Chiavaroli C, Hannaert P. Therapeutic efficacy and mechanism of action of ethamsylate, a long-standing hemostatic agent. *American Journal of Therapeutics* 2006;**13**(3):236-47. [DOI: 10.1097/01.mjt.0000158336.62740.54.]

Gleeson 1994

Gleeson N. Cyclic changes in endometrial tissue plasminogen activator and plasminogen activator inhibitor type 1 in women with normal menstruation and essential menorrhagia. *American Journal of Obstetrics and Gynecology* 1994;**171**(1):178-83. [PMID: 8030696]

GRADEpro GDT 2015 [Computer program]

GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), accessed prior to 28 April 2022. Available at gradepro.org.

Hallberg 1966

Hallberg L, Hogdahl A, Nilsson LM, Rybo G. Menstrual blood loss - a population study. Variation at different ages and attempts to define normality. *Acta Obstetetrica et Gynecologica Scandinava* 1966;**45**(3):320-51. [DOI: 10.3109/00016346609158455]

Harlow 2004

Harlow S, Campbell OM. Epidemiology of menstrual disorders in developing countries: a systematic review. *British Journal of Obstetricas and Gynecology* 2004;**111**(1):6-16. [PMID: 14687045]

Harrison 1976

Harrison RF Campbell S. A double-blind trial of ethamsylate in the treatment of primary and intrauterine-device menorrhagia. *Lancet* 1976;**308**(7980):283-5. [DOI: https://doi.org/10.1016/S0140-6736(76)90733-9]

Haththotuwa 2011

Haththotuwa R, Goonewardene M, Desai S, Senanayake L, Tank J, Fraser I. Management of abnormal uterine bleeding in low- and high-resource settings: consideration of cultural issues. *Seminars in Reproductive Medicine* 2011;**29**(5):446-58. [DOI: 10.1055/s-0031-1287668]

Herman 2013

Herman MC, van den Brink MJ, Geomini PM, van Meurs HS, Huirne JA, Eising HP, et al. Levonorgestrel releasing intrauterine system (Mirena) versus endometrial ablation (Novasure) in women with heavy menstrual bleeding: a multicentre randomised controlled trial. *BioMed Central Womens Health* 2013;**13**:32. [DOI: 10.1186/1472-6874-13-32]

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2021

Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page MJ. Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook. [www.training.cochrane.org/handbook]

Hurskainen 2007

Hurskainen R, Grenman S, Komi I, Kujansuu E, Luoto R, Orrainen M, et al. Diagnosis and treatment of menorrhagia. *Acta Obstetetrica et Gynecologica Scandinava* 2007;**86**(6):749-57. [DOI: 10.1080/00016340701415400]

Jacobsten 2014

Jacobstein R, Polis CB. Progestin-only contraception: injectables and implants. *Best Practice & Research: Clinical Obstetrics & Gynaecology* 2014;**28**(6):795-806. [DOI: 10.1016/j.bpobgyn.2014.05.003]

Jick 1995

Jick SS, Myers MW. A study of danazol's safety. *Pharmacotherapy* 1995;**15**(6):740-1. [PMID: 8602381]

Karlsson 2014

Karlsson T, Marions L, Edlund M. Heavy menstrual bleeding significantly affects quality of life. *Acta Obstetrica et Gynecologica Scandinava* 2014;**93**(1):52-7. [DOI: 10.1111/aogs.12292]

Kumar 2016

Kumar V, Chodankar R, Gupta J. Endometrial ablation for heavy menstrual bleeding. *Women's Health* 2016;**12**:45-52. [DOI: 10.2217/whe.15.86]

Laberge 2015

Laberge P, Leyland N, Murji A, Fortin C, Martyn P, Vilos G, et al. Endometrial ablation in the management of abnormal uterine bleeding. *Journal of Obstetrics and Gynaecology Canada* 2015;**37**(4):362-79. [DOI: 10.1016/s1701-2163(15)30288-7]

Lecker I 2016

Lecker I, Wang D, Whissell P, Avramescu S, Mazer D, Orser B. Tranexamic acid–associated seizures: causes and treatment. *Annals of Neurology* 2016;**79**:18-26. [PMID: 26580862]

Liu 2007

Liu Z, Doan Q, Blumenthal P, Dubois R. A systematic review evaluating health-related quality of life, work impairment, and health-care costs and utilization in abnormal uterine bleeding. *Value in Health* 2007;**10**(3):183-94. [DOI: 10.1111/j.1524-4733.2007.00168.x]

Micks 2013

Micks EA, Jensen JT. Treatment of heavy menstrual bleeding with the estradiol valerate and dienogest oral contraceptive pill. *Advances in Therapy* 2013;**30**(1):1-13. [DOI: 10.1007/s12325-012-0071-3]

Miller 2015

Miller J, Lenhart G, Bonafede M, Basinski C, Lukes A, Troeger K. Cost effectiveness of endometrial ablation with the NovaSure (R) system versus other global ablation modalities and hysterectomy for treatment of abnormal uterine bleeding: US commercial and Medicaid payer perspectives. *International Journal of Women's Health* 2015;**7**:59-73. [DOI: 10.2147/ijwh.s75030]

Morrison 2008

Morrison J, Patel S, Watson W, Zaidi Q, Mangione A, Goss T. Assessment of the prevalence and impact of anemia on women hospitalized for gynecologic conditions associated with heavy uterine bleeding. *Journal of Reproductive Medicine* 2008;**53**(5):323-30. [PMID: 18567277]

Munro 2012

Munro M, Critchley H, Fraser I. The FIGO systems for nomenclature and classification of causes of abnormal uterine bleeding in the reproductive years: who needs them? *American Journal of Obstetetrics and Gynecology* 2012;**207**(4):259-65. [DOI: 10.1016/j.ajog.2012.01.046]

Munro 2018

Munro M. Endometrial ablation. *Best Practice & Research Clinical Obstetrics & Gynaecology* 2018;**46**:120-39. [DOI: https://doi.org/10.1016/j.bpobgyn.2017.10.003]

NICE 2007

National Institute for Health and Clinical Excellence. Heavy Menstrual Bleeding. Clinical Guideline No. 44. National Collaborating Centre for Women's and Children's Health

Commissioned by the National Institute for Health and Clinical Excellence 2007. [https://www.nice.org.uk/guidance/cg44]

NICE 2018a

National Institute for Health and Clinical Excellence. Heavy Menstrual Bleeding. Clinical Guideline No. 88. National Collaborating Centre for Women's and Children's Health Commissioned by the National Institute for Health and Clinical Excellence 2018. [https://www.nice.org.uk/guidance/ng88/evidence]

NICE 2018b

RCOG, National Guideline Alliance, hosted by the Royal College of Obstetrician and Gynaecologists. Evidence reviews for management of heavy menstrual bleeding. National Institute for Health and Clinical Excellence 2018. [file:///P:/FMHSfiles/network%20meta-analisis/NICE%20NMA%20HMB.pdf]

Pincus 1899a

Pincus L. Response to the article of Mr Duhrssen about "autmocausis" [Erwiderung auf den Aufsatz des Herrn Duhrssen uber “Atmocausis”]. *Centralblatt für Gynäkologie* 1899;**13**:352.

Pincus 1899b

Pincus L. Some remarks on the article on Zestocausis the Treub's Clinic [Einege Bemerkungen zu dem Aufsatz Zestocausis aus der Treub'schen Klinic]. *Centralblatt für Gynäkologie* 1899;**4**:113.

Puhan 2014

Puhan M, Schünemann H, Hasan Murad, M, Li T, Brigardello-Petersen R et al, GRADE working group. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;**349**:g5630. [DOI: //doi.org/10.1136/bmj.g5630]

RCOG 2012

Royal College of Obstetricians and Gynaecologists. National Heavy Menstrual Bleeding Audit. London: RCOG; 2012. Second Annual Report. [https://www.rcog.org.uk/en/news/rcog-release-four-year-national-audit-shows-improved-treatment-for-women-with-heavy-menstrual-bleeding-hmb/]

Rees 1987

Rees M, DiMarzo V, Tippins J, Morris H, Turnbull A. Leukotriene release by endometrium and myometrium throughout the menstrual cycle in dysmenorrhoea and menorrhagia. *Journal of Endocrinology* 1987;**113**(2):291-5. [PMID: 3035052]

Review Manager 2020 [Computer program]

Review Manager 5 (RevMan 5). Version 5.4. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2020. [https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman]

Salanti 2014

Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JP. Evaluating the quality of evidence from a network meta-analysis. *PLOS ONE* 2014;**9**(7):e99682. [DOI: 10.1371/journal.pone.0099682]

Santesso 2020

Santesso N, Glenton C, Dahm P, Garner P, Akl E, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. Journal of Clinical Epidemiology 2020;**119**:126-35. [DOI: Journal of Clinical Epidemiology]

Shaw 1972

Shaw S, Aaronson D, Moyer D. Quantitation of menstrual blood loss- further evaluation of the alkaline hematin method. *Contraception* 1972;**5**(6):497-513. [DOI: 10.1016/0010-7824(72)90015-7]

Shea 2007

Shea B, Grimshaw J, Wells G, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *Bio Med Central Medical Research Methodology* 2007;**7**:10. [DOI: 10.1186/1471-2288-7-10]

Shea 2017

Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;**257**:j4008. [DOI: https://doi.org/10.1136/bmj.j4008]

Smith 1981

Smith SK, Abel MH, Kelly RW, Baird DT. Prostaglandin synthesis in the endometrium of women with ovular dysfunctional uterine bleeding. *British Journal Obstetrics & Gynaecology* 1981;**88**(4):434-42. [PMID: 7225303]

Speroff 2010

Speroff L, Darney P. Clinical Guide for Contraception. Philadelphia: Lippincott Williams & Wilkins (LWW), 2010. [ISBN: 978-1-60-831610-6]

Tanaka 2013

Tanaka E, Momoeda M, Osuga Y, Rossi B, Nomoto K, Hayakawa M, et al. Burden of menstrual symptoms in Japanese women: results from a survey-based study. *Journal of Medical Economics* 2013;**16**(11):1255-66. [DOI: 10.3111/13696998.2013.830974]

Uhm 2014

Uhm S, Perriera L. Hormonal contraception as treatment for heavy menstrual bleeding: a systematic review. *Clinical Obstetrics and Gynecology* 2014;**57**(4):694-717. [DOI: 10.1097/grf.0000000000000061]

Van der Heijden 2017

Van der Heijden P, Geomini P, Herman M, Veersema S, Bongers M. Timing of insertion of levonorgestrel-releasing intrauterine system: a randomised controlled trial. *British Journal of Obstetrics and Gynecology* 2016;**124**(2):299-305. [DOI: 10.1111/1471-0528.14445]

Van Valkenhoef 2016

Van Valkenhoef G, Dias S, Ades AE, Welton N. Automated generation of node-splitting models for assessment of

inconsistency in network meta-analysis. *Research Synthesis Methods* 2016;**7**(1):80-93. [DOI: 10.1002/jrsm.1167]

White 2015

White IR. Network meta analysis. *Stata Journal* 2015;**15**:951-85. [https://www.stata-journal.com/article.html?article=st0410]

Yepes-Nunez 2019

Yepes-Nunez J, Lic SA, Guyatta G, Jacka SM, Brozek JL, Beyenea J, et al. Development of the summary of findings table for network meta-analysis. *Journal of Clinical Epidemiology* 2019;**115**:1-13. [DOI: https://doi.org/10.1016/j.jclinepi.2019.04.018]

ADDITIONAL TABLES

Table 1. Characteristics of studies contributing data to the network meta-analysis of first-line treatments

Study	Interventions				Inclusion	Exclusion	Outcomes
	A	B	C	D			
(D) Agarwal 2016	COC (20 µg of ethinyl oestradiol and 120 µg of desogestrel)	Combined vaginal ring	—	—	• 18 to 50 years • Any fibroids < 5 cm, no other pelvic pathology • Not on hormonal therapy during last 3 months	• Fibroids > 5 cm; adenomyosis • Smoker • Pregnant or desirous of pregnancy • Any contraindication to hormonal treatment	• PBAC • Hb • Adverse events • Overall satisfaction with treatment • Treatment success (PBAC score reduced to < 100)
(D) Ashraf 2017	Long-cycle progestogen (Norethisterone)	LNG-IUS	—	—	• Women aged 18-45 with dysfunctional uterine bleeding measuring PBAC > 100 points for 2 consecutive cycles • Uterus size < 10 cm on ultrasonography • Negative cervical cytology on Pap smear	• Contraindications for levonorgestrel intrauterine system and norethisterone use • Pregnancy • Post-menopausal bleeding • Uterine neoplastic disease • Patients with concomitant use of medications that could influence the study objectives • Intramural or subserous fibroids of mean diameter > 4 cm or submucous fibroids • Adenomyosis, or endometrial abnormalities • Coagulation disorders, liver disease or pelvic inflammatory disease	• PBAC baseline 3 and 6 months
(D) Bonduelle 1991	Luteal progestogen (Norethisterone 5 mg 3 times/day, day 19 to 26 of the cycle)	Danazol (200 mg daily)	—	—	• Complaint of MBL requiring more than 5 pads/tampons per day for cycle longer than 6 days • Presence of flooding or clots on any day of the cycle	• Underlying pathology (from history, examination and D & C within the last year)	• Duration of menstruation (days) • Prevalence of side effects

Table 1. Characteristics of studies contributing data to the network meta-analysis of first-line treatments *(Continued)*

					• Presence of secondary anaemia • Excessive menstrual loss proving socially and domestically disruptive		
(D) Bonnar 1996	Tranexamic acid regular dose (3-4 g/day)	Ethamsylate	NSAIDs (mefenamic acid)	—	• Women reporting HMB confirmed to have > 80 mL per cycle loss • Normal cervical smear 3 to 12 months before commencing the study	• Organic causes of menorrhagia found at hysteroscopy or endometrial biopsy • Previous renal or hepatic impairment • VTE, inflammatory bowel disease, peptic or intestinal ulceration, coagulation or fibrinolytic disorders	• Menstrual blood loss: objective measurement (alkaline haematin method) • Duration of blood loss (days) • Participant's estimate of blood loss • Number of sanitary towels used (end scores and change scores) • Dysmenorrhoea • Side effects
(D) Buyru 1995	Danazol	Luteal progestogen (Norethisterone)	—	—	• Women aged 25 to 50 years, with menorrhoea using pads for more than 3 days	• Organic pathology	• Days of menstrual bleeding and adverse events
(D) Callender 1970	Tranexamic acid regular dose (3-4 g/day)	Placebo	—	—	• HMB, either as described by the participant or participants presenting with iron deficiency anaemia presumed to be due to HMB	• Significant clinical abnormality (from gynaecological examination) or significant histological abnormality (from dilatation and curettage)	• Menstrual blood loss by total body counter: 2 µg to 4 µg of Cu ^{59}Fe given intravenously and total body count measured at 2-weekly intervals throughout the study • Blood loss estimated from loss of radioactivity multiplied by the total blood volume (end scores and change scores)

Table 1. Characteristics of studies contributing data to the network meta-analysis of first-line treatments *(Continued)*

							• Duration of bleeding in days and number of pads used • Side effects reported
(D) Cameron 1990	Luteal progestogen (Norethisterone)	NSAIDs (mefenamic acid)	—	—	• 21 to 51 years • Menstrual blood loss > 80 mL/cycle over 2 cycles measured by the alkaline haematin method	• Organic disease • Non-ovulatory cycles • Non-compliance with collecting pads	• Menstrual blood loss • Number of days bleeding • Cycle length • Side effects • Patient compliance
(D) Chamberlain	NSAIDs (mefenamic acid)	Ethamsilate	—	—	• 18 to 55 years, with menorrhagia (menstrual blood loss > 80 mL/cycle) and regular menstrual cycles	• Taking oral contraceptives, antacids, anticoagulants or protein-bound drugs • Hepatic impairment, inflammatory bowel disease or endocrine disorders • Wish to become pregnant during trial • Known allergies to prostaglandin inhibitors • Anaemic (haemoglobin < 9 g/dL) • IUS fitted • Uterine enlargement due to fibroids	• Menstrual blood loss (mean of 3 Rx cycles measured by alkaline haematin method) • Menstrual blood loss (during 1 post Rx cycle measured by the same method) • Adverse events
(D) Dahiya 2016	COC (30 µg ethinyl estradiol and 150 µg levonorgestrel)	Combined vaginal ring	—	—	• Women 18 to 50 years of age • Fibroids < 4 cm; no other pelvic pathology • Not on hormonal therapy for the last 6 months	• Known or suspected malignant condition of genital tract or breast • Lactating • Any liver or heart disease • Arterial or venous thrombosis • Headache with focal neurological symptoms • Severe hypertension	• PBAC • Adverse events • Acceptability

Table 1. Characteristics of studies contributing data to the network meta-analysis of first-line treatments *(Continued)*

					• Personal or family history of any bleeding disorder • Vaginal or cervical infection; cervical descent • Chronic constipation		
(D) Dockeray 1989	NSAIDs (mefenamic acid)	Danazol	—	—	• Objective unexplained menstrual blood loss > 80 mL/cycle (alkaline haematin method) • History of excessive menstrual bleeding • Normal pelvic organs and no endometrial pathology	Not stated	• Menstrual blood loss (alkaline haematin method) • Number of days bleeding • Quality of life (dysmenorrhoea) • Adverse events (incidence, severity) • Patient acceptability of treatment (prepared to continue Rx?)
(D) Dunphy 1998	Danazol	Luteal progestogen (medroxyprogesterone acetate)	—	—	• Women aged 31 to 54 years with HMB > of 80 mL/cycle • Willing to use barrier methods of contraception	• Treatment contraindication and pregnancy	• PBAC at 3 months follow up • Side effects • Withdrawal from treatment
(D) Edlund 1995	Kabi pro Tranexamic 600 mg	Kabi Protranexamic 1200 mg	Placebo	—	• Over 80 mL per cycle blood loss, regular cycles • Normal-sized uterus on clinical examination	• Renal or hepatic impairment • Clinical pelvic pathology or cervical intra-epithelial neoplasia • Concomitant disease or medication affecting menstruation • VTE, haematological or coagulation disorders • Dilatation and curette within the previous 2 months • Inability to comply with the protocol	• Menstrual blood loss: objective (alkaline haematin method) as absolute measurement and relative change from baseline • Duration of loss (days) • Number of sanitary towels used • Participant's subjective assessment (end scores and change scores)

Table 1. Characteristics of studies contributing data to the network meta-analysis of first-line treatments *(Continued)*

							• Side effects reported
(D) Endrikat 2009	LNG-IUS	COC (20 µg ethinyl estradiol and 1 mg NETA)	—	—	• Otherwise healthy women, aged > 30 years at entry • Diagnosis of idiopathic menorrhagia • Normal or only slightly enlarged uterus	• Contraindications for LNG-IUS and combined oral contraceptive pills • Metabolic and endocrine diseases • Diagnostically unclassified genital bleeding • History of liver or vascular diseases • Concomitant use of medications that could influence study objectives • Intramural or subserous fibroids of mean diameter ≥ 4 cm or submucous fibroids, adenomyosis, or endometrial abnormalities (verified by saline infusion sonography or hysteroscopy) • Perimenopausal women (as evidenced by serum FSH levels > 50 IU/L and serum estradiol levels < 100 pmol/L)	• PBAC • Treatment success (menstrual blood loss < 100 mL at 12 months) • Hb • Quality of life (menorrhagia severity score) • Adverse events
(D) Fraser 1981	NSAIDs (mefenamic acid)	Placebo	—	—	• 14 to 48 years with a convincing history of menorrhagia, but with a variety of menorrhagia diagnoses: ovulatory dysfunctional uterine bleeding (DUB) (N = 28), anovulatory DUB (N = 6), IUS (N = 6), fibroids (N = 2), tubal sterilisation (N = 25), oral contraceptive pill (N = 1) and von Willebrand disease (N = 1)	• Not stated	• Menstrual blood loss (alkaline haematin method) • Menstrual symptoms (graded 0 to 3) - data not available for subgroup • Adverse events - data not available for subgroup

Table 1. Characteristics of studies contributing data to the network meta-analysis of first-line treatments *(Continued)*

					• Results reported in review only for the subgroup of patients with ovulatory menorrhagia (N = 28)		
(D) Fraser 1991	COC (30 µg ethinyl estradiol and 150 µg levonorgestrel)	NSAIDs (naproxen)	NSAIDs (mefenamic acid)	Danazol	• History of menorrhagia and regular periods	• Pelvic pathology	• Menstrual blood loss (measured by alkaline haematin method) • Immediate side effects
(D) Fraser 2011	COC (Estradiol valerate and dienogest)	Placebo	—	—	• Aged over 18 years, symptoms of heavy prolonged and/or frequent menstrual bleeding • Willing to use a barrier method of contraception and to use and collect sanitary protection items for the duration of the study • Normal result from endometrial biopsy or at most, mild simple endometrial hyperplasia in the 6 months prior to study entry • Use of iron supplementation allowed if considered necessary by the attending physician	• Abnormal transvaginal ultrasound; abnormal values for any laboratory examination considered clinically significant • History of endometrial ablation; had undergone dilatation and curettage in the 2 months preceding the study • Bleeding disorder that was determined during the run-in phase to be the result of organic pathology • Unwilling to discontinue the use of tranexamic acid or NSAIDs during menses • BMI > 32 kg/m^2 • Aged 35 years 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	• Complete response to Rx (complete return to 'normality': no bleeding episodes lasting more than 7 days; no more than 4 bleeding episodes overall; no bleeding episodes with a blood loss volume of 80 mL or more; no more than 1 bleeding episode increase from baseline; no more than 24 days of bleeding overall; and no increase from baseline in the total number of bleeding days) • Changes in menstrual blood loss volume; Hb • Proportion of participants with an improvement in menstrual bleeding symptoms

Table 1. Characteristics of studies contributing data to the network meta-analysis of first-line treatments *(Continued)*

							• Adverse events
(D) Freeman 2011	Tranexamic acid low dose (< 2.5 g/day)	Tranexamic acid regular dose (3-4 g/day)	Placebo	—	• 18 to 49 years old • 'History of cyclic HMB', confirmed by alkaline haematin method during the 2 pre-treatment cycles • Normal pelvic examination and Pap smear • Normal transvaginal ultrasound	• 'Clinically significant disease' • Anovulatory dysfunctional uterine bleeding, metrorrhagia, menometrorrhagia, polymenorrhoea • Endometrial polyps, hyperplasia or carcinoma • Cervical carcinoma. • Myocardial infarction, abnormality on electrocardiography, ischaemic disease, stroke, transient ischaemic attack • VTE, or coagulopathy, currently taking anticoagulants, aspirin, dong quai, aminocaproic acid, hydroxychloroquine • Serum prolactin > 30 µg/L, uncontrolled hypothyroidism • Severe anaemia (Hb < 8 g/dL) • History of bilateral oophorectomy or hysterectomy • Pregnancy, breastfeeding, planning to become pregnant during the study, or became pregnant during the study or currently taking hormonal contraceptives • Fibroids were only excluded if they were thought to require surgical management	• Menstrual blood loss: alkaline haematin method (change scores) • Subjective improvements in menstrual blood loss: MIQ (i.e. QoL) • Side effects/adverse drug effects: 'adverse events monitoring' (conducted at each study visit); physical examination; electrocardiograph; vital signs; and laboratory evaluation
(D) Goshtasebi 2013	Tranexamic acid low dose (<2.5 g/day)	Long cycle progestogen (medroxi progesterone acetate)	—	—	• 20 to 45 years old • reported regular HMB • BMI 19 to 29	• 'Organic cause of HMB' • Iron-deficiency anaemia • Previous VTE • History of chronic diseases	• Subjective assessment of menstrual blood loss, using a modified PBAC (end scores)

Table 1. Characteristics of studies contributing data to the network meta-analysis of first-line treatments *(Continued)*

						• History of diseases known to interfere with menstrual bleeding (e.g. fibroids, anticoagulant use, COC or other hormonal drug use) • IUS in situ	• Serum Hb and ferritin • SF-36 for QoL (Farsi version) • HMB questionnaire (Farsi version) • Side effects
(D) Grover 1990	NSAIDs (mefenamic acid)	Placebo	—	—	• Subjective complaint of menorrhagia and normal cervical cytology and secretory endometrium (after dilation and curettage)	• Local pelvic causes of bleeding	• 'Relief' of menorrhagia (perception of improvement) • Number of days bleeding
(D) Hashim 2012	Combined vaginal ring	Long cycle progestogen (norethisterone)	—	—	• HMB based on a PBAC score > 185 (mean of 2 control cycles) • Parous women desiring contraception and willing to use a male condom if required • Aged between 20 and 35 years in good general health and with a regular menstrual cycle with evidence of ovulation diagnosed when midluteal phase serum progestogen level was ≥ 5 ng/mL Normal pelvic examination with a sound measurement of the uterus of < 10 cm • No pathology from pelvic US	• Pregnancy • Age > 35 years • Obesity (BMI > 30 kg/m^2 • Smokers • Current intrauterine device users • Abnormal uterine bleeding not fully investigated • Hormone therapy or any medication that might affect menstrual blood loss within the previous 3 months • Women who used injectable hormones for contraception during the previous 12 months • Use of drugs that interfere with contraceptive hormone metabolism • Previous endometrial resection/ablation and other pathology (fibroids of any size etc) • HMB of endocrine or systemic origin (e.g. thyroid disease and coagulopathies)	Primary • PBAC score at the end of Rx Secondary • Hb, adverse events, quality of life (measured by HRQoL-4), overall satisfaction

Table 1. Characteristics of studies contributing data to the network meta-analysis of first-line treatments *(Continued)*

					• Normal histology on endometrial biopsy • Negative cervical smear • No contraindications to either treatment	• Participants unwilling to use contraception or medical management	
(D) Higham 1993	Luteal progestogen (norethisterone)	Danazol (has 2 different danazol dosages that for the NMA were combined in one group)	—	—	• Menstrual blood loss > 80 mL/cycle • Regular cycle between 21 and 35 days • Aged 20 to 50 years • Weight 45 to 110 kg • Endometrial sampling within previous 3 years • No sensitivity to danazol or NET or ingestion 10 weeks previously • Informed consent	• Underlying pathological conditions (from clinical assessment, pelvic US or endometrial biopsy) • Concomitant treatment with hormonal, anti-prostaglandin or anti-coagulant medication • Pregnancy or lactation or desire to become pregnant • Perimenopausal • IUS wearers	• Menstrual blood loss (alkaline haematin method) • Improvement in menstrual blood loss (patient assessment) • Duration of menstruation • Side effects • Treatment acceptability
(D) Irvine 1988	Long-cycle progestogen (norethisterone)	LNG-IUS	—	—	• > 80 mL/cycle loss, as measured by alkaline haematin method • Parous (1 or more children) • Normal pelvic examination • Negative cervical cytology • Regular menstrual cycle • Good general health • Uterine cavity sound length less than 10 cm	• Abnormal pelvic examination • Recent use of oestrogens • Progestogens or anticoagulants (within 3 months) • Injectable hormones for contraception (within 12 months)	• Menstrual blood loss (alkaline haematin method • Hb and serum Fe • Participant symptom/side effect questionnaire • Participant satisfaction • How their periods interfered with their quality of life before and after treatment • Proportion of women with amenorrhoea • Proportion of women with specified side effects

Table 1. Characteristics of studies contributing data to the network meta-analysis of first-line treatments *(Continued)*

							• Withdrawal from treatment because of adverse events relating to treatment • Acceptability of treatment (willingness to continue)
(D) Jaisamrarn 2006	Tranexamic acid regular dose (3-4 g/day)	Luteal progestogen (norethisterone)	NSAIDs (mefenamic acid)	—	• Women aged 18 to 45 years • Regular menstrual cycle (21 to 35 days) • Serum progesterone during 5 to 9 days before menstruation of ≥ 5.0 ng/mL • PBAC score > 130 during run-in phase • No contraindication to treatment drugs • Normal renal and liver function, normal pelvic examination	• Concomitant diseases, organic disease • VTE, haemorrhagic or fibrinolytic disorder • Hormone therapy during last 3 months or taking any medication that might affect menstrual blood loss • Need or desire for contraception • Need for iron supplementation • Inability to comply and no consent	• Menstrual blood loss using PBAC (end scores) • Cure rate (success rate) (defined as PBAC ≤ 130) • Adverse events • QoL using a standardised questionnaire • Acceptability of treatment • Hb • Duration of menstruation
(D) Jensen 2011	COC (estradiol valerate and dienogest)	Placebo	—	—	• Over 18 years • HMB, prolonged menstrual bleeding, frequent menstrual bleeding or any combination • Willing to use a barrier method of contraception and to use (and collect) all sanitary protection items (pads and tampons) provided to them for use during the study • Normal endometrial biopsy or, at	• Abnormal transvaginal ultrasound at screening (fibroids or polyps whose size or localisations would be associated with HMB) • Clinically significant abnormal values for any laboratory examination • Endometrial ablation or dilatation and curettage in the 2 months before the study • Organic pathology • Use of agents intended for treatment of symptoms of abnormal uterine bleeding • BMI > 32 kg/m^2	• Complete response to Rx (complete return to 'normality': no bleeding episodes lasting more than 7 days; no more than 4 bleeding episodes overall; no bleeding episodes with a blood loss volume of 80 mL or more; no more than 1 bleeding episode increase from baseline; no more than 24 days of bleed-

Table 1. Characteristics of studies contributing data to the network meta-analysis of first-line treatments *(Continued)*

					most, mild simple endometrial hyperplasia during the 6 months before study entry • Women over 40 years had to have FSH level < 40 milli-international units/mL • Use of iron supplementation allowed if the attending physician considered it necessary	• Smoking > 10 cigarettes per day (in women older than 35 years) • Criteria consistent with contraindications for the use of COC	ing overall; and no increase from baseline in the total number of bleeding days) • Changes in menstrual blood loss volume; Hb • Proportion of participants with an improvement in menstrual bleeding symptoms • Adverse events
(D) Kaunitz 2010	Luteal progestogen (medroxy progesterone acetate)	LNG-IUS	—	—	• Parous women aged 18 years or more • Idiopathic heavy menstrual bleeding (≥ 80 mL per cycle (assessed by alkaline haematin method) • Desiring intrauterine contraception • Willing to use barrier contraception	• Irregular bleeding • Hot flushes • Sleeping disorders • Changes in mood within the 3 months before the study • Breastfeeding • Congenital or acquired uterine abnormality including fibroids if they distorted the uterine cavity or cervical canal • History of organic causes of abnormal uterine bleeding • Use of LNG-IUS or a copper IUS during the 30 days before the study • History of vascular or coagulation disorders • Concomitant use of medication or presence of an underlying disease/condition known to affect the metabolism or pharmacokinetics of the study medication • BMI> 35 kg/m^2	• Absolute change in menstrual blood loss from baseline to end of study • Proportion of women in which the treatment was successful (defined as menstrual blood loss < 80 mL at end of study and ≥ 50% reduction in HMB from baseline) • Adverse events

Table 1. Characteristics of studies contributing data to the network meta-analysis of first-line treatments *(Continued)*

(D) Kiseli 2016	Tranexamic acid regular dose (3-4 g/day)	Luteal progestogen (Norethisterone)	LNG-IUS	—	• Women 18 to 45 years old • PBAC score > 100 during 2-month run-in phase	• Abnormal pelvic ultrasound or endometrial biopsy • Hb < 10 g/dL • Abnormal Pap smear result • Thyroid disease • Hypertension, diabetes, or coronary artery disease • History of previously taking medications for HMB • Contraindication to current therapy	• PBAC score and associated percentage reduction in blood loss (end scores) • World Health Organization QoL-Short Form (Turkish version), in which women report limitations in physical health, psychological status, social support, and 'relating to their environment'
(D) Kriplani 2006	Tranexamic acid low dose (<2.5 g/day)	Long cycle progestogen (Medroxy progesterone acetate)	—	—	• Women presenting with HMB and PBAC score > 100	• Fibroids, adenomyosis, endometriosis, atypia on endometrial histopathology. • Thyroid disease • History of hormone therapy in previous 3 months • Unwilling to trial medical management	• PBAC score and associated percentage reduction in blood loss (end scores) • Recurrence of HMB • Further surgery • Participant satisfaction • Duration of bleeding • Hb level • Side effects
(D) Lukes 2010	Tranexamic acid regular dose (3-4 g/day)	Placebo	—	—	• History of at least 3 days of HMB over at least 4 of their last 6 cycles, confirmed during 2 cycles before treatment phase commenced • Normal pelvic examination and Pap smear	• History of significant medical problem • Severe anaemia (Hb < 8 g/dL) • Pregnant/lactating • Endometrial abnormalities • Cervical carcinoma • Anovulatory dysfunctional uterine bleeding • Glaucoma, ocular hypertension	• Objective measurement of menstrual blood loss: alkaline haematin method (change scores) • Subjective improvements in menstrual blood loss: MIQ; occurrence of large blood stains • Hb and ferritin concentrations

Table 1. Characteristics of studies contributing data to the network meta-analysis of first-line treatments *(Continued)*

					• No clinically important findings on transvaginal ultrasound • Willingness to use non-hormonal contraception during the trial	• Use of anticoagulants; aspirin, dong quai; aminocaproic acid, hydroxychloroquine • Uterine fibroids were only an exclusion criteria if thought to require surgical management	• Side effects
(D) Muggeridge 1983	NSAIDs (mefenamic acid)	Placebo	—	—	Menstrual blood loss > 75 mL/cycle	Pelvic pathology	Menstrual blood loss (alkaline haematin method) Dysmenorrhoea (numerical score) Adverse events
(D) Preston 1995	Tranexamic acid regular dose (3-4 g/day)	Luteal progestogen (Norethisterone)	—	—	• Cycle length 28 ± 7 days • Average menstrual loss over 2 cycles > 80 mL per cycle • No hormone therapy within 3 months • No medication which may affect menstrual blood loss • Confirmed to be ovulating; and had complied with the protocol during the 2 months of placebo treatment	• Abnormal renal function, pelvic examination or cervical smear • Anovulatory cycles • Lack of compliance during the placebo cycles	• Objective menstrual blood loss (alkaline haematin method) • QoL assessed using a questionnaire (at end of cycle 2 and cycle 4) using 5-point scale for general health, amount of flooding and leakage experienced, abdominal pain, limitation to social life, effect on sex life • Diary of days bleeding, number of sanitary towels used and side effects recorded by participants
(D) Sayed 2011	LNG-IUS	COC (30 µg ethinyl estradiol and 150 µg levonorgestrel)	—	—	• 20 to 50 years old, heavy menstrual bleeding, regular cycle, • Lived sufficiently close to hospital for follow-up	Pregnancy History of ectopic pregnancy, puerperal sepsis, pelvic inflammatory disease Evidence of defective coagulation,	• Reduction of HMB (%) (PBAC and alkaline haematin assessment) at 12 months • Hb and ferritin levels

Table 1. Characteristics of studies contributing data to the network meta-analysis of first-line treatments *(Continued)*

					• Requested contraception	Abnormalities on ultrasound (including submucous fibroids of any size distorting the cavity of the uterus or intramural or subserous fibroids > 5 cm in diameter) History of malignancy or evidence of hyperplasia in the endometrial biopsy Incidental adnexal abnormality on ultrasound Previous endometrial ablation/resection Uninvestigated postcoital bleeding, untreated abnormal cervical cytology Contraindication to COCs.	• Quality of life (HRQoL) • Treatment failure
(D) Shabaan 2011	COC (30 µg ethinyl estradiol and 150 µg levonorgestrel)	LNG-IUS	—	—	• 20 to 50 years old at initial assessment • Regular cycle • Self-described HMB • Requested contraception • Living nearby to make follow-up possible	• Pregnancy; history of ectopic pregnancy; puerperal sepsis; pelvic inflammatory disease • Evidence of defective coagulation • Ultrasound abnormalities and fibroids of any size, incidental adnexal abnormality on ultrasound • History or evidence of malignancy or hyperplasia in the endometrial biopsy • Contraindications to COC • Previous endometrial ablation or resection • Uninvestigated postcoital bleeding and untreated abnormal cervical cytology	• Treatment failure (need for medical or surgical treatment during follow-up) • Menstrual blood loss (alkaline haematin method and PBAC) • HB levels • Lost days as a result of impaired physical or mental health (QoL)
(D) Tsang 1987	NSAIDs (mefenamic acid)	Placebo	—	—	Women aged 26 to 47 years with either a history of heavy menstrual bleeding or menstrual blood loss > 80 mL/cycle (measured	Use of hormonal contraceptives or anti-inflammatory drugs and use of intrauterine contraceptive device	Menstrual blood loss (measured by alkaline haematin method)

Table 1. Characteristics of studies contributing data to the network meta-analysis of first-line treatments *(Continued)*

					objectively) and regular menstrual cycles		
(D) van Eijkeren 1992	NSAIDs (mefenamic acid)	Placebo	—	—	• < 45 years • Menstrual blood loss > 80 mL/cycle • Regular menstrual cycle	• Intrauterine device • Use of non-steroidal anti-inflammatory drugs (NSAIDs) or other medication that could affect haemostasis • Contraindications against NSAIDs • Use of hormonal medication	• Menstrual blood loss (alkaline haematin method) • Adverse events
(D) Ylikorkala 1986	NSAIDs (naproxen)	Placebo	—	—	Menstrual blood loss > 80 mL/cycle Regular cycles and normal pelvic findings	Not stated	• Menstrual blood loss (alkaline haematin method) • Subjective perception of improvement in menstrual blood loss • Adverse events (any vs none)
(D) Zhang 2008	Tranexamic acid regular dose (3-4 g/day)	Luteal progestogen (Norethisterone)	—	—	• Proven ovulatory menorrhagia, attending gynaecological clinics • PBAC score > 130	• Heart, kidney, liver or haematological disease • Having had any hormonal treatments in the 3 months prior, including an IUS • Previous thrombo-embolus	• Menstrual blood loss (PBAC) • Length of menstrual period • 6-item QoL questionnaire collected in the 2nd week before, during and after each treatment cycle and a 3rd (follow-up) cycle

COC: combined oral contraceptive; **D & C**: dilation and curettage; **FSH**: follicle-stimulating hormone; **HMB**: heavy menstrual bleeding; HRQoL: health-related quality of life; **IUS**: intrauterine system; **LNG-IUS**: levonorgestrel-releasing intrauterine system; **MIQ**: Menorrhagia Impact Questionnaire; **NET**: norethisterone; **NETA**: norethisterone acetate; **NMA**: network meta-analysis; **NSAIDs**: non-steroidal anti-inflammatory drugs; **PBAC**: pictorial blood assessment chart; **QoL**: quality of life; **VTE**: venous thromboembolism.

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments

Study	Interventions		Inclusion criteria	Exclusion criteria	Outcomes	Comments
	A	B				
(D) Abbott 2003	Bipolar NREA (Novasure)	Balloon NREA (Cavaterm)	• Abnormal uterine bleeding • PBAC > 150 • No intrauterine pathology demonstrated by inpatient or outpatient hysterectomy • Normal endometrial biopsy; uterine length < 12 cm • Premenstrual gonadotropin levels • Normal Pap smear • Completed their family	• None reported	• Amenorrhoea • Menstrual change • QoL, sexual activity • Patient satisfaction • Procedure acceptability	—
(D) Athanatos 2015	Microwave NREA	Bipolar NREA (Novasure)	• Women with HMB with PBAC > 150 for longer than 1 year • Family planning completed • < 50 years of age • FSH < 20 IU/mL	• Uterine or endometrial pathology (ultrasound and biopsy) • Coagulopathies and thyroidal dysfunction	At 3 months: • Amenorrhoea rate • Need for analgesia post ablation • Dysmenorrhoea rate • Improvement in clinical condition • Satisfaction At 12 months: • Amenorrhoea rate • PBAC • Improvement in daily life • Need for other intervention	All participants received GnRH 3 months pretreatment
(D) Barrington 2002	LNG-IUS	Balloon NREA (Thermachoice)	Women with menorrhagia refractory to medical treatment referred by GPs to gynaecology clinic in district hospital	Cavity > 12 cm; subserous fibroids; malignant or pre-malignant pathology (from endometrial biopsy)	• PBAC score at 6 months • Improvement in bleeding • Requirement for further treatment (surgical)	GnRH 1 month pretreatment on the EA arm
(D) Bhattacharya 1997	Laser REA	TCRE/ rollerball	• HMB, ≤ 50 years of age • < 100 kg in weight	None reported	• Operative complications	—

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

			• Clinical diagnosis of dysfunctional uterine bleeding • Uterus < size of at pregnancy at 10 weeks and normal endometrial histology • (the original study included hysterectomy as one of the arms, and participants were hysterectomy candidates		• Postoperative recovery • Relief of menstrual and other symptoms • Need for further surgical treatment • Satisfaction with treatment • Differential resource use	
(D) Bongers 2004	Bipolar NREA (Novasure)	Balloon NREA (Thermachoice)	• Menorrhagia (PBAC ≥ 150) • Normal uterus with benign histology and uterine length 6 to 11 cm • Normal PAP smear • Negative chlamydia test • FSH < 40 IU/L	• Coagulopathies • Treatment with anticoagulation • Desire to preserve fertility • Prior uterine surgery (except low-segment caesarean section)	Primary: • Amenorrhoea at 3, 6, and 12 months, and later follow-up at 5 years Secondary: • Duration of surgery • Satisfaction • Re-intervention rates (hysterectomy) • Dysmenorrhoea rates • Proportion with blood clots • Health-related quality of life	—
(D) Brun 2006	Balloon NREA (Cavaterm)	TCRE REA	• Women with menorrhagia unresponsive to medical treatment requesting conservative surgical management • No longer wishing to become pregnant • PBAC score > 100 • Internal uterine cavity length 4-12 cm • Normal endometrial biopsy • Normal cervical cytology • Completed family	• Endometrial malignancy • Active pelvic infection • Submucous fibroids • Polyps; uterine malformation • History of endometrial ablation • Hormone treatment (GnRHa or danazol) in previous 6 months	Primary: • Amenorrhoea rates • PBAC scores Secondary: • Satisfaction • Safety (technical complication rate, duration of surgery; clinical complications (intraoperative and postoperative)) • Pain scores • Hospital stay • Resumption of normal or work activities	—

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

			• Using a reliable method of contraception		• Additional surgery	
(D) Clark 2011	Bipolar NREA (Novasure)	Balloon NREA (Thermachoice)	• Women presenting to gynaecology outpatient clinic with HMB without organic pathology • No response to previous medical therapy • No desire to preserve fertility • No contraindications to endometrial ablation (uterine cavity length > 11 cm; previous open myomectomy, end ablation, or resection and classical C-section)	• < 25 years • Perimenopausal (FSH ≥ 40 IU/L) • Suspected of having genital tract infection • Significant uterine pathology (from preoperative endometrial biopsy and imaging by transvaginal ultrasound or diagnostic hysteroscopy) – included submucous fibroids and fibroids outside the uterine cavity > 3 cm in diameter	Primary: • Amenorrhoea rate at 6 months Secondary: • Satisfaction • QoL • Technical feasibility (failed procedure, operative complications, duration of surgery) • Acceptability • Improvement in dysmenorrhoea • Improvement in premenstrual syndrome	Novasure versus Thermachoice III
(D) Cooper 1999	Microwave NREA	TCRE + Rollerball REA	• Premenopausal • Completed their families • Dysfunctional uterine bleeding (uterine size equivalent to 10 weeks' pregnancy or less) • Informed consent	Histopathological abnormalities of the endometrium	Primary: • Participant satisfaction with and acceptability of treatment Secondary: • Menstrual status • Quality of life • Morbidity • Duration of surgery • Intraoperative complications • Postoperative pain relief • Postoperative stay • Absence from work	—
(D) Cooper 2002	Bipolar NREA (Novasure)	TCRE + Rollerball REA	• Menorrhagia verified by validated PBAC = 150 for 3 consecutive months • History of failed medical therapy	• Bacteraemia, sepsis, or other active systemic infection • Active or recurrent chronic	• PBAC • Procedure time • Sedation • Intraoperative adverse events • Postoperative adverse effects	—

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

				pelvic inflammatory disease • Symptomatic endometriosis • History of uterine surgery that would have interrupted integrity of the uterine wall • Previous endometrial ablation • Abnormal Pap smear and/or endometrial biopsy • Taking anticoagulants • Hormone contraceptives or drugs that could thin myometrial muscle like long-term steroids • Desire future childbearing/preservation of fertility • Abnormal or obstructed uterine cavity		
(D) Cooper 2004	Microwave NREA	Rollerball REA	• Non-pregnant women > 30 years • No desire for future pregnancy • Failed, refused, or did not tolerate medical treatment • PBAC ≥ 185 (previous 1 or 3 months) • FSH ≤ 30 IU/L • Uterine cavity 6 to 14 cm	• Myometrial wall thickness < 8 mm • Active endometriosis • Endometrial hyperplasia • Endometrial cancer • Active PID • Previous endometrial ablation • Previous caesarean section (classical scar) • History of gynaecological malignancy in past 5 years • Untreated or unevaluated cervical dysplasia	Primary: • PBAC < 75 Secondary: • Amenorrhoea • Duration of surgery • Anaesthesia • Complications • Adverse events • Dysmenorrhoea • Quality of life (SF-36) • Satisfaction • Acceptability	All participants received 1 month GnRh pretreatment

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

				• Known clotting defects or bleeding disorders • IUS		
(D) Cooper 2019	NREA (either Thermal balloon or radiofrequency)	Minimally invasive hysterectomy (Laparoscopic supracervical hysterectomy, LASH)	• Women under 50 years • No desire for further children • Referred to gynaecology for surgical treatment of HMB • Inclusion criteria were eligibility for endometrial ablation (fibroids <3 cm, uterine cavity size <11 cm, and absence of endometrial pathology on biopsy) and normal cervical cytology.	Previous endometrial ablation If laparoscopic surgery was contraindicated, or if they were unable to give informed consent or complete trial paperwork	Primary • Menorrhagia multi-attribute scale (MMAS) • Satisfaction at 12 months post surgery • Incremental cost (to the health service) per quality-adjusted life year (QALY) gained (LASH versus EA) Secondary outcome measures • MMAS at 6 months • Satisfaction at 6 months • Acceptability of procedure measured at 6 weeks • Severity of post-operative pain at 1 to 14 days and at 6 weeks • Generic health related quality of life (SF-12, EQ-5D 3-L) measured at baseline, 6 and 12 months • Sexual Activity Questionnaire (SAQ) at baseline, 6 and 12 months • Duration of operation • Peri-operative complications and recovery details including analgesia requirements • Time to discharge • Further gynaecological surgery by 12 months	—

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

(D) Corson 2000	Electrode balloon NREA (Vesta)	TCRE + rollerball REA	• Score ≥ 150 on the PBAC • No plan for more children • Either using contraception or one of either partner sterilised • Failed progestin therapy or refused medical therapy or showed intolerance to these agents	• FSH levels > 40 IU/mL • Distorted uterine cavities • Myomas or polyps • Cavity in excess of 9.75 cm • Significant systemic medical disease • Pregnancy; pelvic inflammatory disease • Carcinoma; clotting defects • Previous unsuccessful endometrial ablation • Myomectomy • Uterine reconstruction • Long-acting hormone therapy within 3 months of enrolment • Hyperplasia of the endometrium	• PBAC scores post Rx • Proportion with amenorrhoea • Proportion with successful Rx (defined as PBAC < 76) • Adverse events	—
(D) Corson 2001	Hydrotermablation NREA (Hydro Thermablator)	Rollerball REA	• 30 to 50 years • Family planning complete • Documentation of excessive bleeding • Uterine cavity measuring ≤ 10.5 cm • History of ineffective, not tolerated, or refused medical therapy	• Active or symptomatic pelvic inflammatory disease • Intramural myomas > 4 cm • Submucous myomas or polyps	• Reduction in menstrual diary blood loss scores • Success of treatment (PBAC score < 75) • Amenorrhoea rates • Quality of life scores • Adverse events • Need for further surgery • Operative complications • Need for analgesia	—
(D) Crosignani 1997	Rollerball REA	Minimally invasive hysterectomy (Vaginal hysterectomy)	• ≤ 50 years • HMB not responding to medical treatment and refereed for hysterectomy • Mobile uterus with volume < 12 weeks in gestational size	• Known PID or endometriosis • Urinary stress incontinence or moderate/severe genital prolapse.	• Participant satisfaction with treatment • Improvement in menstrual blood loss • Quality of life	—

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

			and < 380 mL on ultrasound • Negative cervical smear, no evidence of atypical hyperplasia at endometrial biopsy • No adnexal tumours at clinical and ultrasound examination	• Clotting disorders, use of IUS or drugs that may affect menstrual blood loss • Unstable general conditions • Submucous myomas > 3 cm in diameter or > 50% intramural extension	• Duration of surgery (minutes) • Duration of hospital stay (days) • Return to work (weeks) • Requirement for further surgery	
(D) Crosignani 1997a	Rollerball REA	LNG-IUS	• HMB (diagnosed by history, haemoglobin and iron levels and PBAC score ≥ 100 month for 2 months as per menstrual diary) • Normal uterus on hysteroscopy and ≤ volume of 8-week • Normal endometrial pathology on biopsy • Family complete, not breastfeeding	• Women < 38 years • Hormonal treatment over past 6 months • Serious concomitant illness • Myoma > 3 cm diameter	Primary outcome • Reduction in menstrual bleeding at 1 year, measured by PBAC. • Other outcomes Amenorrhoea/oligomenorrhoea rates • Health-related quality of life: SF-36 • Treatment satisfaction • Additional treatment received • Adverse effects • Haemoglobin level	—
(D) De Souza 2010	LNG-IUS	Balloon NREA (Thermachoice)	• Clinical HMB refractory to medical treatment (OC, HT, NSAIDs) • 3-month washout period, regular menstrual cycles • Age ≥ 35 years • Menstrual blood loss > 80 mL (as measured by PBAC) • Negative pregnancy test • Uterine volume < 200 mL (as measured by transvaginal sonogram) • Negative Pap smear within past year	Not reported	• Menstrual blood loss (PBAC score) • Other bleeding outcomes (amenorrhoea, decreased bleeding) • Hb levels • Quality of life (Psychological General Wellbeing Index) • Failure of treatment • Satisfaction rates	—

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

			• No intracavity abnormalities, pelvic inflammatory disease, suspected endometrial pathology, abnormal endometrial histology, previous endometrial resection and ablation, or any other pathology for which hysterectomy would be appropriate • Women were required to have completed their families			
(D) Dickersin 2007	Endometrial ablation (any method)	Hysterectomy (unspecified)	• 18 years of age or older; premenopausal • Dysfunctional uterine bleeding for at least 6 months (defined as one or more of excess duration, amount or unpredictability) • Refractory to medical treatment for at least 3 months	• Postmenopausal • Bilateral oophorectomy • Pregnant • Wishing to retain fertility • Refusal to consider surgery	• Pain, bleeding and fatigue at 1 year • QoL outcomes • Sexual function • Employment, housework, leisure activities • Out-of-pocket costs, health provider visits • Surgical complications • Additional surgery	Resectoscopic endometrial ablation with electrodesiccation/coagulation or vaporisation OR NREA ablation with thermal balloon. Hysterectomy vaginal, laparoscopic or abdominal abdominal
(D) Duleba 2003	Cryoablation NREA	Rollerball REA	• Menorrhagia due to benign causes • Good general health • Documented history of excessive uterine bleeding for at least 3 months • Failed traditional therapy • Did not desire future fertility • PBAC > 150	• Uterine volume > 300 mL • Uterine cavity sounding > 10 cm • Clotting deficit or bleeding disorders • Active pelvic inflammatory disease • Abnormal cervical cytology within 1 year • History of gynaecological malignancy within 5 years • Intramural myomas > 2 cm,	• Menstrual diaries 1 cycle before and 12 months after • PBAC • Bleeding • Pain • Mood • PMS • QoL - Dartmouth COOP assessment questionnaire • Anaesthesia • Adverse outcomes • Satisfaction	—

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

				submucous myomas, or endometrial polyps • Septate uterus • Previous endometrial ablation or other surgery in which thinning of the uterine wall may occur • Malignant pathology or hyperplasia • Pregnancy		
(D) Dwyer 1993	TCRE REA	Open hysterectomy	• < 52 years of age. • Complaint of menorrhagia that could not be controlled by conservative means • Candidates for abdominal hysterectomy	• Uterine size over 12 gestational weeks • Additional symptoms or other pathology, making hysterectomy the preferred treatment	• Satisfaction with surgery at 4 months and 2.8 years • Change in menstrual blood loss after surgery (subjective) at 4 months and 2.8 years • Quality of life at 2.8 years • Postoperative complications • Duration of hospital stay (days) Duration of surgery (minutes) • Return to work (weeks) • Requirement for further surgery within one and 2.8 years • Total health service resource cost at 4 months and at 2.8 years	Participants on the EA arm received medroxyprogesterone six weeks pretreatment.
(D) Ergun 2012	LNG-IUS	Rollerball REA	• Women with abnormal uterine bleeding which had not responded to medical treatment • Under 35 years of age • Regular menstrual cycle • Score of 100 on PBAC	• Ongoing pregnancy • Pelvic infection • Abnormality in the uterus, uterine cavity and/or suspicious endometrial histology (screened by TVUS) • Abnormal cervical or endometrial histology	• PBAC scores • Further surgical treatment • Failure of treatment • Amenorrhoea and hypomenorrhoea • Satisfaction • Hb levels	—

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

				• Pathology that might require a hysterectomy • Contraindication to administration of anaesthetic agents • Desire to preserve fertility		
(D) Gannon 1991	TCRE REA	Open hysterectomy	Women waiting for abdominal hysterectomy for menorrhagia	• Leiomyomata • Endometrial or cervical neoplasia • Concomitant ovarian pathology • Pelvic inflammatory disease or endometriosis	• Change in menstrual blood loss • Duration of surgery (minutes) and duration of hospital stay (days) • Return to work (weeks) • Postoperative complications • Requirement for further surgery • Resource cost of surgery (theatre and ward) (per woman)	—
(D) Ghazizadeh 2014	Bipolar NREA (Novasure)	TCRE REA	• Menorrhagia; hysterectomy candidate • Age 35 to 45 • Hormonal treatment for at least 6 months without adequate improvement	• Pregnancy; null gravid; abnormal Pap smear; genital infection • Hormonal disorder • Hormonal treatment • Anomalous uterus • Any disorder inside the uterine cavity or abnormal endometrial biopsy • Coagulative disorder • Submocusal myomas > 2 cm and intramural myomas that moved the endometrial layer • Uterine cavity > 11 cm	• Decreased menstrual blood loss • Interaction between bleeding and normal activity • Anaemia (estimated 6.8 mg/dL as cut-off for anaemia) • Patients' satisfaction (checklist 6 months' follow-up; some up to 12)	—

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

(D) Hawe 2003	Balloon NREA (Cavaterm)	Laser REA	• Normal endometrial biopsy • No intrauterine pathology • Normal uterine cavity (uterine length < 12 cm) • High on blood loss score (> 100) • Normal cervical cytology • Completed family and using contraception	• Endometrial hyperplasia and malignancy • Active pelvic infection • Intrauterine pathology	• Amenorrhoea rate, then effect on menstrual status • Questionnaire assessing menstrual symptoms • QoL • Sexual activity • Procedure satisfaction and acceptability - included questionnaires EQ-5D, SF-12, SAQ; VAS; pain VAS • Operative details and morbidity	Cavaterm YAGlaser
(D) Herman 2013	Bipolar NREA	LNG-IUS	• Women with HMb • Over 34 years • Without intracavitary pathology • Not planning future pregnancy	None reported	• PBAC at 24 months • Re intervention • Satisfaction • Quality of life • Sexual function	—
(D) Hurskainen 2004	Hysterectomy (unspecified)	LNG-IUS	• Women premenopausal with HMB • Age 35 to 49 • Family complete • Suitable for either treatment (elegible for hysterectomy)	• Submucous fibroids, endometrial polyps, ovarian tumours or cysts > 5 cm diameter • Cervical disease, urinary and bowel symptoms or pain caused by large fibroids • Lack of indication for hysterectomy • Intermenstrual bleeding as main complaint • Previous unsuccessful treatment with LNG-IUS • History of cancer • Severe depression • Acne	Primary • Health-related quality of life by EuroQol EQ-5D questionnaire Other outcomes • Quality of life by RAND 36-item health survey • Objective bleeding (alkaline haematin method), amenorrhoea/oligomenorrhoea rates. • Health-related quality of life (RAND 36-item health survey and EuroQol EQ-5D questionnaire) • Menopausal symptoms (Kupperman test of menopausal distress) • General health on VAS (0 to 100) • Anxiety (Finnish version of Spielberger State-Trait Anxiety Inventory)	Hysterectomies were either abdominal, vaginal or laparoscopic)

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

					• Sexual functioning (McCoy Sex Scale) • Adverse effects • Cost-effectiveness • Haemoglobin	
(D) Istre 1998	TCRE REA	LNG-IUS	• Women aged 30 to 49 years with HMB, referred by GP for surgery • PBAC score > 75 for 2 months before randomisation • Family complete • Regular uterine cavity ≤ 10 cm in length	• Breastfeeding or current pregnancy • Subserous myoma > 40 mm diameter • Use of hormonal medication within past 3 months • History of thrombo-embolic disease or liver disease • Any abnormal intrauterine pathology • Pelvic inflammatory disease within past 6 months or current infection	• Treatment success: PBAC ≤ 75 at 12 months, no re-surgery in TCRE group, no removal of device in LNG-IUS group • Amenorrhoea/oligomenorrhoea rates • Quality of life on a VAS • Additional treatment received • Adverse effects	—
(D) Jain 2016	Balloon NREA (LiNA-Menotreat system)	Minimally invasive hysterectomy (Vaginal)	• Women over 40 years, no desire for future childbearing • HMB PBAC score≥100 • Uterine size up to 14 weeks of pregnancy • leiomyomas of 5 cm in diameter or less • Uterocervical length of 12 cm or less	• Acute pelvic inflammatory disease or pelvic pathology (e.g. adenomyosis, gynaecologic cancers, including endometrial malignancy) • Atypical endometrial hyperplasia • Submucosal leiomyomas were excluded	• Amenorrhoea and hypomenorrhoea at 1,6,12 and 24 months • Requirement of further HT • Haemoglobin level at 6 months • Operative time, blood loss • Intraoperative and postoperative events (VAS up to 72 hrs post procedure, adverse events) • Hospital stay • Improvement from baseline • UFS-QoL scores.	Ht vaginal
(D) Kittelsen 1998	LNG-IUS	TCRE REA	• Women aged 30 to 49 years with HMB recruited from a gynaecology clinic specialising in operative hysteroscopy	• Hormone treatment in past 3 months • Previous history of DVT, throm-	• Women aged 30 to 49 years with heavy menstrual bleeding recruited from a gynaecology clinic	—

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

			• Premenopausal (FSH > 40 IU/mL and 17B oestradiol < 0.2 nmol/mL) • Score of > 100 on PBAC with a regular uterine cavity	boembolism or liver disease • Uncertain about future wish for pregnancy • Pregnancy or breastfeeding • Fibroids • Endometrial pathology • Congenital or acquired uterine anomaly • Current infection or PID within last 6 months • Endometriosis or adenomyosis	specialising in operative hysteroscopy • Premenopausal (FSH > 40 IU/mL and 17B oestradiol < 0.2 nmol/mL) • Score of > 100 on PBAC with a regular uterine cavity	
(D) Laberge 2017	Bipolar NREA (Minerva)	Rollerball REA	• Premenopausal (FSH level 40 IU/mL) • 25 to 50 years of age • Have completed childbearing • To provide alkaline haematin documented evidence of HMB (PALM-COEIN: E, O). minimum bleeding level 160 mL per cycle (for 1 cycle) to qualify for study participation • Uterine sounding length limited to maximum 10 cm • Agree to not use any hormonal birth control to eliminate the possibility of post-treatment bleeding reduction induced by the suppressive action of hormonal contraceptives	• PID. Active/acute endometritis • Sexually transmitted infection • Bacteraemia, sepsis, other active local and/or systemic infection • Untreated/unevaluated cervical dysplasia (except cervical intraepithelial neoplasia I) • Endometrial hyperplasia • Known or suspected abdominal or pelvic cancer • Coagulopathies-Anticoagulation therapy • Congenital malformations of the uterus • Hysteroscopically or ultrasonographically confirmed fibroid(s) distorting the uterine cavity • Endometrial polyp(s) larger than 2 cm	• Menstrual blood loss: success (alkaline haematin < 80 mL) • Amenorrhoea rate at 12 months • Satisfaction • Surgery duration (minutes) • Safety in terms of adverse effects • Requirement for further surgery or medical treatment • Dysmenorrhoea reduction • PMS reduction	—

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

				• Less than 6 weeks' postpartum • History of prior uterine surgery (except low-segment cesarean delivery) • Previous endometrial ablation • Having implantable contraceptive device • Medications that could thin the myometrial muscle such as long-term steroid use (except inhaler or nasal therapy for asthma)		
(D) Malak 2006	TCRE REA	LNG-IUS	• Premenopausal women aged 40 to 50 years with regular uterine cavity, no wish for pregnancy. • Spontaneous cycles, scheduled for hysterectomy for excessive uterine bleeding (PBAC score > 100 monthly) with or without dysmenorrhoea	• Fibroid > 3 cm diameter, > 3 fibroids on ultrasound • Possible malignancy or active liver disease • Adnexal tumours/cysts • Pelvic inflammatory disease with past 12 months	• Treatment success with primary intervention (PBAC score < 75 at 12 months), no removal of LNG-IUS or repeat surgery • Quality of life (by EuroQol - visual analogue scale: EQ-VAS) • Adverse events	—
(D) McClure 1992	Laser REA	TCRE REA	• Subjective diagnosis of menorrhagia unresponsive to medical therapy • Normal cervical cytology • menstrual blood loss ≥ 70 mL (alkaline haematin method)	• Fibroid enlargement • Other intrauterine pathology	• Reduction in menstrual blood loss • Duration of surgery • Postoperative complications and requirement for analgesia • Need for further surgery • Amenorrhoea rate	
(D) Meyer 1998	Balloon NREA (Thermachoice)	Rollerball REA	• 30 years or older and premenopausal • Normal Pap smears • Normal endometrial biopsies within last 6 months	• Submucous fibroids • Suspected genital tract infection or malignancy	• Satisfaction rate • Improvement in dysmenorrhoea symptoms • Proportion with PMS after treatment	—

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

			• History of 3 months of excessive uterine bleeding (PBAC score ≥ 150) • Ineffective medical therapy • Uterine cavity normal (by hysterosalpingography, hysteroscopy, or TSS) with a range between 4 and 10 cm • No desire for future fertility; willing to continue current contraception	• Previous endometrial ablation	• Inability to work • PBAC score • Complication rate • Duration of surgery • Requirement for additional surgery	
(D) O'Connor 1997	TCRE REA	Hysterectomy (unspecified)	• Women 30 to 50 years of age, decision to have no more children. • Regular menstrual cycles of between 21 and 35 days, with each period lasting for less than 50% of the cycle • Documented evidence of normal endometrial histology within the previous 12 months and normal cervical smear within the previous 3 years	• Serious intercurrent illness • Intermenstrual or postcoital bleeding • Uterine size corresponding to pregnancy of greater than 12 weeks of gestation, submucous fibroids larger than 5 cm in diameter • Adnexal tenderness that is suggestive of pelvic inflammatory disease or endometriosis • Major uterovaginal prolapse or severe urinary symptoms • Severe premenstrual syndrome or menopausal symptoms	• Satisfaction rate at 2 years • Duration of surgery (minutes) and duration of hospital stay (days) • Difficulty of surgery (this outcome not entered in the review) • Complication rate • Requirement for further surgery	Hysterectomies: 28 abdominal and 28 vaginal. Outcomes not reported by type of hysterectomy
(D) Ozdegirmenci 2011	LNG-IUS	Open hysterectomy	Not specifically reported - women with adenomyosis by sonogram and MRI with menorrhagia and or dysmenorrhoea (all women had menorrhagia)	• Endometrial pathology • Fibroids: submucous, intramural or subserous > 2 cm • Postmenopausal status • Pelvic inflammatory disease	• Quality of life (WHO Quality of Life - Short Form, Turkish Version (WHOQoL-BREF TR) at 12 months • Aligomenorrhoea at 12 months • Side effects • Hb levels	—

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

				• Malignancy or suspicion of malignancy • Thromboembolism • Desire to become pregnant • Cardiac or hepatic disease • Use of oral progestogen during previous 3 months • Contraindications to MRI		
(D) Pellicano 2002	Balloon NREA (Cavaterm)	TCRE REA	• Age < 50 years • Weight < 100 kg • Not desiring pregnancy • History of ≥ 3 months failed medical Rx • Evidence of normal endometrial histology/Pap smear within previous 12 months	• Uterine size > 12 weeks' pregnancy • Submucosal fibroids • Adnexal masses or endometriosis • Uterovaginal prolapse and severe urinary symptoms • Severe intercurrent illness	Primary: • Satisfaction rate at 3 months, 1 year, and 2 years Secondary: • Duration of surgery • Intraoperative blood loss • Requirement for further surgery • Postoperative pain • Hospital stay • Complications • Resumption of normal activity	—
(D) Penninx 2010	Bipolar NREA (Novasure®)	Hydrothermablation NREA (Hydro ThermAblator®)	• Women with menorrhagia (defined by Higham minimum score of 150 points) • Normal uterine cavity (length 6 to 12 cm and histologically benign endometrium) • Normal Pap smear • Negative Chlamydia test • Premenopausal (FSH < 40 IU/L) • Desire for ablation after looking at other options for Rx	• Presence of coagulopathies • Use of anticoagulants • Desire to preserve fertility • Prior uterine surgery (except low-segment CS) • Suspected or confirmed uterine malignancy	Primary: • Amenorrhoea at 12 months after surgery Secondary: • Reduction in bleeding • Patient satisfaction • Complications • Re-intervention for hysterectomy	
(D) Penninx 2016	Bipolar NREA (Novasure®)	Balloon NREA (Thermablate®)	• Women with HMB PBAC > 150 points and follicle-stimulating hormone (FSH) level < 40 IU/L	• Coagulopathies or use of anticoagulants • Desire to preserve fertility.	• PBAC • Amenorrhoea rate • Pain • Satisfaction	

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

			• Normal uterine cavity (cavity length 6 to 12 cm), confirmed by saline infusion sonography or diagnostic hysteroscopy • No endometrium pathology (histologically benign; confirmed within 6 months of screening by endometrium in the office (Pipelle1, CooperSurgical, Trumbull, USA) • Normal Pap smear	• Prior uterine surgery other than low-segment caesarean section • (Suspected) uterine malignancy. • Preferred to be treated in an outpatient setting • US with intracavitary pathology, except for women with intracavitary polyps < 1 cm	• Requirement for further treatment	
(D) Perino 2004	Laser thermal ablation NREA (ELITT (endometrial laser intrauterine thermal therapy)	TCRE REA	• Dysfunctional uterine bleeding not associated with organic pathology and not responding to medical treatment	not reported	Primary: • Amenorrhoea and other menstrual status • Satisfaction rates Secondary: • Intraoperative complication rate • Operation time • Pain • Further treatment with hysterectomy	
(D) Pinion 1994	Endometrial Ablation (unspecified)	Hysterectomy (*)	• Women under 50 years and weight less than 100 kg. • Clinical diagnosis of dysfunctional uterine bleeding, uterus < 10 weeks of gestational size, normal endometrial histology	not reported	• Satisfaction rate at one and four years • Change in general health and MBL Duration of surgery (minutes) and duration of hospital stay (days) • Return to work (weeks) • Complication rate • Quality of life (Hospital Anxiety and Depression Scale, Golombok Rust Inventory of Marital State) • Health service costs at one and four years • Participant costs at one year • Requirement for further surgery	Laser ablation or TCRE. EA arm received GnRh for 5 weeks pretreatment
(D) Romer 1998	Balloon NREA (Cavaterm®)	Rollerball REA	• Recurrent menorrhagia not responsive to medical therapy • No desire for future fertility	• Intrauterine abnormality • Fibroids • Hyperplasia	• Satisfaction rate • Amenorrhoea or hypomenorrhoea rate	

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

(D) Sambrook 2009	Microwave NREA (MEA™)	Balloon NREA (Tball)	• Women reporting heavy menstrual loss and requesting endometrial ablation • Premenopausal • Completed their families • Uterine size equivalent to a 12-week pregnancy or less • No histopathological abnormalities • No fibroids obstructing the uterine cavity • Lower-segment caesarean section if scar thickness > 10 mm on transvaginal US	not reported	Primary: • Satisfaction (6-point scale) and menstrual scores at 1 year (PBAC) Secondary: • Operative differences • Acceptability of treatment • Health-related quality of life	
(D) Sesti 2011	Balloon NREA (Tball)	Minimally invasive hysterectomy (Laparoscopic subtotal hysterectomy)	• PBAC score ≥ 100 (average of two consecutive cycles) • Completed family • Normal smear • Pelvic ultrasound scan and endometrial biopsy	• Previous endometrial resection/ablation or levonorgestrel intrauterine system • Any uterine pathology on pelvic ultrasound scan or hysteroscopy. • Any pathology whereby hysterectomy was indicated • Uninvestigated abnormal bleeding or postmenopausal bleeding.	Primary: • Menstrual bleeding (PBAC score) at three, six, 12 and 24 months Secondary: • Quality of life (SF-36 score) at 24 months • Improvement in bleeding patterns (frequency and duration of bleeding) at three, six, 12 and 24 months • Haemoglobin levels at three, six, 12 and 24 months • Intensity of postoperative pain • Early postoperative complications	endometrial ablation via Thermachoice® III thermal balloon ablation laparoscopic subtotal hysterectomy
(D) Sesti 2012	Minimally invasive hysterectomy (Laparoscopic subtotal hysterectomy)	LNG-IUS	• Women with HMB PBAC > or = 100 (average of 2 cycles) unresponsive to medical treatment • Age 35 to 50 years, completed family • Failed appropriate first-line oral medical therapy • Normal PAP smear; no pelvic pathology on US; normal endometrial biopsy.	• Previous endometrial resection/ablation or insertion of LNG-IUS • Uterine pathology on scan or hysteroscopy • Pathology where hysterectomy indicated • Postmenopausal bleeding	Primary: • Satisfaction (6-point scale) and menstrual scores at 1 year (PBAC) Secondary: • Operative differences • Acceptability of treatment • Health-related quality of life	
(D) Shaw 2007	Balloon NREA (Menotreat)	LNG-IUS	•Women with idiopathic menorrhagia aged 25 to 49 years in whom prior appropriate oral	•Previous LNG-IUS or endometrial resection/ablation	•Change in PBAC score at 12 months (median and range)	

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

			medical treatment had failed. •Family complete •Normal histology, normal ultrasound (fibroids up to 2.5 cm OK), normal cervical smear, PBAC score > 120 (mean over 2 cycles)	•Abnormal uterine bleeding, other pathology, submucous fibroid •Uterine cavity < 7 cm or over 11 cm	•Changes in Hb and ferritin at 6 months •Patient satisfaction •Hysterectomy rate at 2 years •Treatment discontinuation (e.g. for adverse events, menorrhagia, LNG-IUS expulsion)	
(D) Soysal 2002	Balloon NREA (Uterine Balloon Therapy system ™ , Gynecare)	LNG-IUS	•Women aged over 40 with menorrhagia who refused or did not respond to medical treatment. •PBAC scores of > 150 for 2 consecutive months before randomisation •Family complete •Normal blood tests, transvaginal ultrasonography, hysteroscopy, endometrial suction biopsy or cervical smear examination •No intramural or subserous myomas > 2 cm diameter •Regular uterine cavity ≤ 8-week pregnancy and < 190 ml on ultrasonography	•Any medical disorder other than iron deficiency anaemia •Abnormal intrauterine pathology	•PBAC reduction and haemoglobin •Health-related quality of life: SF-36, HAD depression scale •Treatment satisfaction •Additional treatment received •Adverse effects	Participants on the EA arm received 2 months of GnRH analogues pretreatment.
(D) Talis 2006	Balloon NREA (Thermachoice®)	LNG-IUS	• Women 25 to 50 years, with self described HMB who had completed their family and regular cycle.	•U.S. Submucosal fibroids, intramural fibroids > 3 cm diameter, large subserosal fibroids, endometrial polyps. •Lab: Follicle-stimulating hormone level (FSH) > 30 IU/l, adverse endometrial histology. •Hysteroscopy: submucosal fibroids, endometrial polyps. •Adnexal abnormality on ultrasound. •Severe inter-menstrual bleeding, severe dysmenorrhoea or severe premenstrual pain, chronic pelvic pain. •Medical contraindications to	•PBAC •Satisfaction •Quality of life and menstrual symptoms, measured by questionnaire •Haemoglobin level •Treatment side effects •Treatment failure (for the LNG-IUS this was confirmed expulsion, completed removal or the initiation of alternative therapy. For thermal balloon ablation this was the initiation of medication or the completion of alternative surgery, such as hysterectomy). •Direct and indirect costs of treatment, subsequent medical treatment, lost income	

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

				either study treatment •Previous endometrial ablation or resection •Uninvestigated post-coital bleeding or untreated abnormal cervical cytology	and medical treatment for failed procedures.
(D) Tam 2006	Balloon NREA (Thermachoice®)	LNG-IUS	•Women aged over 40 years with a documented history of excessive menstrual bleeding for at least 3 months, family complete. •Prior oral medical treatment unsuccessful, not on any hormonal treatment	•Uterus > 10 weeks' gravid size, submucosal fibroids, endometrial polyps. •Contraindications to interventions. Possible malignancy	•Menstrual pattern at 1 year (self reported) •Adverse effects •Haemoglobin and iron status •Health status: SF-36 (using norms for Hong Kong Chinese)
(D) van Zon-Rabelink 2003	Balloon NREA (Thermachoice®)	Rollerball REA	• Menorrhagia without sufficient relief from medical therapy by GP • Menstrual blood loss score = 185 points in 2 periods due to dysfunctional uterine bleeding according to US and diagnostic hysteroscopy	not reported	• Technical safety aspects • Reduction in menstrual bleeding • Success rate (PBAC < 185) • Satisfaction
(D) Vercellini 1999	Vaporising REA	TCRE REA	• > 35 years • Referred for hysterectomy • Uterine volume < 12-week pregnancy • Normal uterine cavity at hysteroscopy • No evidence of atypical hyperplasia • No adnexal tumours on clinical and ultrasonographic examination	• Women uncertain about future children • Recent use of hormonal agents or drugs that might affect menstrual blood loss • Intramural or subserous fibroids of ≥ 3 cm • "Unstable" general conditions	• Extent of absorption of distension fluid • Duration of surgery • Difficulty of surgery • Satisfaction rate • Proportion with amenorrhoea • Proportion with amenorrhoea and hypomenorrhoea • PBAC score
(D) Zupi 2003	TCRE REA	Minimally invasive hysterectomy (Laparoscopic subtotal hysterectomy)	•Women with HMB unresponsive to medical treatment, younger than 50 years of age; weight less than 100 kg. •Not seeking contraception •Normal endometrial histology and Pap	not reported	•Pain (immediately after surgery and then for a week) •Duration of vaginal bleeding •Date resumed normal activities, sexual intercourse, work •Quality of life (SF-36) •Further surgery

Table 2. Characteristics of studies contributing data to the network meta-analysis of second-line treatments *(Continued)*

	smear within the previous six months •Uterus not greater than 12 weeks of pregnancy in size; without submucosal fibroids, adnexal masses or endometriosis	•Operative outcomes (duration of surgery, blood loss, complications, hospital stay)

DVT: deep vein thrombosis; **EA**: endometrial ablation; **FSH**: follicle-stimulating hormone; **GnRH**: gonadotropin releasing hormone; **HMB**: heavy menstrual bleeding; **HT**: hormone therapy; **IUS**: intrauterine system; **LNG-IUS**: levonorgestrel releasing intrauterine system; **MMAS**: menorrhagia multi-attribute scale; **NREA**: non-resectoscopic endometrial ablation; **OC**: oral contraceptives; **PBAC**: pictorial blood loss assessment chart; **PID**: pelvic inflammatory disease; **PMS**: premenstrual syndrome; **QoL**: quality of life; **REA**: resectoscopic endometrial ablation; **SAQ**: Seattle Angina Questionnaire ; **SF-12**: Short Form Health Survey; **TCRE**: transcervical endometrial resection; **UFS-QoL**: Uterine Fibroid Symptom Health-Related Quality of Life Questionnaire; **VAS**: visual analogue scale.

Table 3. Review characteristics

Review	Review authors	No. studies (participants)	Participants' characteristics		Interventions-Comparison	Outcomes		LAST SEARCH
			Inclusion criteria	Exclusion criteria		Primary outcomes	Secondary outcomes	
Antifibrinolytics for heavy menstrual bleeding (Bryant-Smith 2018)	• Alison C Bryant-Smith • Anne Lethaby • Cindy Farquhar • Martha Hickey	7 (N = 1312)	Women of reproductive age With regular heavy periods (measured either objectively or subjectively), undertaken at least 2 months' follow-up whilst on treatment, recruited from primary care, family planning, or a specialist clinic setting	• Post-menopausal bleeding • Irregular menses • Intermenstrual bleeding or both • Pathological causes of HMB (e.g. a coagulopathy) • Iatrogenic causes of HMB (e.g. IUS or anti-coagulant medication)	Antifibrinolytics versus: • Placebo • Progestogens • NSAIDs • Ethamsilate • Herbal medicines • LNG-IUS	• Menstrual blood loss (objective or subjective) • Improvement in HMB • Thromboembolic events	• Quality of life • Adverse events	November 2017
Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding (Bofill Rodriguez 2021)	• Magdalena Bofill Rodriguez • Anne Lethaby • Rosalie J Fergusson	10 (N = 1966)	Women of reproductive years with heavy menstrual bleeding (including both heavy regular periods (menorrhagia) and heavy irregular periods (metrorrhagia), measured objectively or subjectively	• Post-menopausal bleeding (> 1 year from the last period) • HMB caused by uterine malignancy or endometrial hyperplasia • Iatrogenic causes of HMB (e.g. intrauterine coil devices)	• Endometrial ablation versus open hysterectomy • Endometrial ablation versus minimally invasive hysterectomy (vaginal or laparoscopic) • Endometrial ablation versus unspecified route of hysterectomy	• Effectiveness (improvement in bleeding: woman's perception, PBAC, requirement of further surgery) • Acceptability (satisfaction) • Safety (adverse events in short and	• Quality of life scores (continuous data) • Quality of life (proportion with improvement) • Duration of surgery • Duration of hospital stay • Time to return to normal activity	September 2019

Table 3. Review characteristics *(Continued)*

						long term)	• Time to return to work • Total health service cost per woman • Total individual cost per woman	
Combined hormonal contraceptives for heavy menstrual bleeding (Lethaby 2019)	• Anne Lethaby • Michelle R Wise • Maria AJ Weterings • Magdalena Bofill Rodriguez • Julie Brown	8 (N = 805)	Women of reproductive years Regular heavy periods measured either objectively or subjectively assessed at baseline for at least one-month follow-up Type of settings: primary care, family planning, or specialist clinic	Not stated	COC versus: • Placebo • NSAIDs • LNG-IUS • CVR CVR versus progestogens	• Menstrual blood loss (treatment success, objectively, semi-objectively or subjectively assessed • Satisfaction	• Adverse events • Quality of life • Haemoglobin	September 2018

Cyclical progestogens for heavy menstrual bleeding
(Bofill Rodriguez 2019b)
	• Magdalena Bofill
	• Anne Lethaby
	• Cindy Low
	• Iain Cameron
		15 (N = 1071)	Women of reproductive age
			Women with regular heavy periods measured either subjectively by the woman, objectively by the alkaline haematin method (more than 80 mL per cycle) or semi-objectively by the pictorial blood assessment chart
			Women attending primary care, family planning or specialist clinics
				• Post-menopausal bleeding (more than one year following the last period)
				• Irregular menses and intermenstrual bleeding
				• Pathological causes of menorrhagia
				• Iatrogenic causes of menorrhagia
					• Progestogen versus placebo
					• Progestogen therapy (luteal phase only) versus
					  ○ NSAIDs
					  ○ Danazol
					  ○ Tranexamic acid
					• Progestogen therapy (norethisterone luteal phase only) versus Pg-IUS and LNG-IUS
					• Progestogen therapy (medrox-
						• Menstrual blood loss (objective or subjective)
						• Satisfaction
							• Days of bleeding
							• Quality of life
							• Compliance
							• Acceptability
							• Adverse events
							• Resource use and cost
								January 2019

Table 3. Review characteristics *(Continued)*

					yprogesterone acetate luteal phase only) versus LNG-IUS • Progestogen therapy (3-4 weeks) versus ○ LNG-IUS ○ Tranexamic acid ○ Combined hormonal vaginal ring ○ Ormeloxifene			
Danazol for heavy menstrual bleeding (Beaumont 2007)	• Heather H Beaumont • Cristina Augood • Kirsten Duckitt • Anne Lethaby	9 (N = 353)	Women of reproductive years Regular (21-35 days cycle) heavy menstrual blood loss, subjectively or objectively defined (for example by alkaline haematin method) Recruitment from primary care, family planning or specialist clinic setting	• Post-menopausal bleeding • Irregular menses and intermenstrual bleeding • Pathological causes of heavy menstrual bleeding	Danazol versus: • Placebo • Progestogens • NSAIDs • COC • Pg-IUS • Different dosages of danazol	• Reduction in menstrual blood loss (objectively or subjectively) • Quality of life • Side effects • Withdrawal due to side effects • Reduction of dysmenorrhoea	• Weight gain • Subjective efficacy of intervention • Time to relapse • Duration of periods • Resource use	April 2007 * Stable
Endometrial resection and ablation techniques for heavy men-	• Magdalena Bofill Rodriguez • Anne Lethaby	28 (N = 4287)	Women of reproductive years with regular heavy periods, measured objectively or subjectively	• Post-menopausal bleeding (longer than 1 year from the last period) • Irregular menstruation and in-	REA versus REA techniques: • Laser ablation versus TCRE	• Menstrual bleeding • Satisfaction	• Operative outcomes • Recovery • Quality of life	May 2018

Table 3. Review characteristics *(Continued)*

strual bleeding (Bofill Rodriguez 2019a)	• Mihaela Grigore • Julie Brown • Martha Hickey • Cindy Farquhar	termenstrual bleeding • Pathological causes of HMB (e.g. uterine cancer) • Iatrogenic causes of HMB (e.g. intrauterine coil devices)	REA versus NREA techniques: • Balloon ablation versus rollerball • Vesta system versus rollerball • Microwave ablation versus TCRE and rollerball • Hydrothermal ablation versus rollerball • Cryoablation versus rollerball • Laser versus TCRE • Electrode ablation versus TCRE plus rollerball • Balloon versus laser • Balloon versus TCRE plus rollerball • Bipolar versus rollerball NREA versus NREA techniques: • Bipolar electrode ablation versus balloon • Bipolar radiofrequency versus hydrothermal ablation • Bipolar electrode ablation versus microwave • Microwave versus balloon ablation	• Adverse events • Requirement of further surgery for bleeding symptoms • Mortality as result of surgery	

Table 3. Review characteristics *(Continued)*

Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding (Bofill Rodriguez 2019c)	• Magdalena Bofill Rodriguez • Anne Lethaby • Cindy Farquhar	25 (N = 759)	Women of reproductive years Regular heavy periods measured either objectively (greater than 80 mL) for one or more cycles prior to the intervention or subjectively by the patient	• Post-menopausal bleeding (less than one year from the last period) • Irregular menses and intermenstrual bleeding • Pathological causes of HMB • Iatrogenic (treatment induced) causes of HMB	NSAIDs versus • Placebo • Tranexamic acid • Ethamsilate • Danazol • Oral progestogens • Pg IUS • COC • 2 different types of NSAIDs	• Menstrual blood loss (objective or subjective) • Quality of life	• Total menstrual fluid loss • Days of bleeding • Adherence to treatment • Acceptability • Adverse events • Resource use/cost	April 2019
Progestogen-releasing intrauterine systems for heavy menstrual bleeding (Bofill Rodriguez 2020)	• Magdalena Bofill Rodriguez • Anne Lethaby • Vanessa Jordan	25 (N = 2511)	Women of reproductive years Regular heavy periods measured either objectively (by the alkaline haematin method), semi-objectively (by PBAC score) or subjectively (patient perception)	• Post-menopausal bleeding • Irregular menses (cycle < 21 days or > 35 days apart) • Intermenstrual bleeding at presentation • Pathological causes of heavy menstrual bleeding • Primary use of progesterone-releasing intrauterine system for any reason other than heavy menstrual bleeding, for example contraception or relief of climacteric symptoms	LNG-IUS versus: • Placebo or no treatment • Any other medical treatment • Endometrial ablation • Hysterectomy	• Reduction of menstrual blood loss (objectively or subjectively) • Satisfaction	• Quality of life • Adverse effects • Withdrawal from treatment because of adverse events or any reason • Treatment failure • Requirement of surgery for the treatment of HMB • Resource cost	July 2019

Table 3. Review characteristics *(Continued)*

Surgery versus medical therapy for heavy menstrual bleeding (Marjoribanks 2016)	• Jane Marjoribanks • Anne Lethaby • Cindy Farquhar	15 (N = 1289)	Women of reproductive age Regular heavy menstrual periods measured either objectively (e.g. via the alkaline haematin test) or subjectively (e.g. via the pictorial blood loss assessment chart (PBAC), a menstrual blood loss diary or according to a woman's personal judgement)	• Post-menopausal bleeding • Irregular menses or inter-menstrual bleeding • Pathological causes of heavy menstrual bleeding • Iatrogenic causes of heavy menstrual bleeding	• Surgery versus oral medication • Surgery versus LNG-IUS	• Menstrual blood loss (objectively or subjectively) • Satisfaction • Adverse events	• Quality of life • Requirement for additional treatment for heavy menstrual bleeding • Cost and resource use	January 2016

COC: combined oral contraceptive; **CVR**: combined vaginal ring; **HMB**: heavy menstrual bleeding; **LNG-IUS**:levonorgestrel-releasing intrauterine system; **NSAIDS**: non-steroidal anti-inflammatory drugs; **PBAC**: pictorial blood assessment chart; **Pg-IUS**: progestogen intrauterine system; **TCRE**: transcervical resection of the endometrium.

Table 4. AMSTAR 2 assessment[a,b,c]

Review	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)
Antifibrinolytics for heavy menstrual bleeding	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Combined hormonal contraceptives for heavy menstrual bleeding	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cyclical progestogens for heavy menstrual bleeding	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
Danazol for heavy menstrual bleeding	+	P	+	P	-	+	+	+	+	+	+	-	-	+	-	+
Endometrial resection and ablation techniques for heavy menstrual bleeding	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table 4. AMSTAR 2 assessment[a,b,c] *(Continued)*

Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Progestogen-releasing intrauterine systems for heavy menstrual bleeding	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Surgery versus medical therapy for heavy menstrual bleeding	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

See Appendix 2 for details.

[a](+) Yes.

[b](P) Partial yes.

[c](-) No.

Table 5. Summary of findings for first-line treatments: mean blood loss (combined data)

Estimated effects, confidence intervals, and certainty of the evidence for menstrual bleeding reduction (mean blood loss at the end of treatment and change from baseline) with first-line treatment

BENEFITS

Patient or population: women with heavy menstrual bleeding

Interventions: non-steroidal anti-inflammatory drugs (NSAIDs), antifibrinolytics, combined oral contraceptive (COC), combined vaginal ring (CVR), luteal cyclical progestogen (luteal Pg), long-cycle progestogen (long-cycle Pg), levonorgestrel intrauterine device (LNG-IUS**),** danazol and ethamsylate

Comparator (reference): placebo (mean blood loss with placebo was 160 U/cycle)

Outcome: menstrual blood loss **(mean blood loss at the end of treatment and change from baseline)**

Setting: clinical

Network geometry plot: Figure 73

Total studies: 26 trials, 1770 women with direct evidence for all comparisons. 8 trials with 710 women compared the interventions versus placebo

Intervention	N trials and N women (direct evidence with comparator)	Relative effect[a] (95% CI) (from network)	Mean difference	Certainty of evidence	Mean rank (1 to 10) and SUCRA[b]
NSAIDs Other direct evidence 5 trials, 205 women Comparing NSAIDs to ethamsylate, antifibrinolytics, luteal Pg and danazol[c]	5 trials, 145 women	−40.67 (−84.61 to 3.27)	Mean blood loss with NSAIDs was 40.67 lower (84.61 lower to 3.27 higher) than placebo	⊕⊕⊖⊖ Low[d,e]	6.4 (SUCRA 40%)
Antifibrinolytics Other direct evidence 4 trials, 358 women Comparing antifibrinolytics to luteal and long-cycle Pg	4 trials, 565 women	−80.32 (−127.67 to −32.98)	**Mean blood loss with antifibrinolytics was 80.32 lower (127.67 to 32.98 lower) than placebo**	⊕⊕⊕⊖ Moderate[e]	3.7 (SUCRA 70%)
COC Other direct evidence 4 trials, 276 women Comparing COC to CVR, LNG-IUS and danazol[c]	No direct evidence with comparator	−56.08 (−140.88 to 28.72)	Mean blood loss with COC was 56.08 lower (140.88 lower to 28.72 higher) than placebo	⊕⊖⊖⊖ Very low[d,f]	5.7 (SUCRA 50%)
CVR Other direct evidence 1 trial, 95 women	No direct evidence with comparator	−81.53 (−177.56 to 14.50)	Mean blood loss with CVR was 81 lower (177.56 lower to 14.5 higher) than placebo	⊕⊖⊖⊖ Very low[d,f]	3.9 (SUCRA 70%)

Table 5. Summary of findings for first-line treatments: mean blood loss (combined data) *(Continued)*

Comparing CVR to long-cycle Pg					
Luteal Pg Other direct evidence 2 trials, 50 women Comparing it to danazol)	No direct evidence with comparator	−19.10 (−87.81 to 49.61)	Mean blood loss with luteal Pg was 19.1 lower (87.81 lower to 49.61 higher) than placebo	⊕⊖⊖⊖ Very low[e,g]	7.8 (SUCRA 20%)
Long-cycle Pg Other direct evidence 1 trial, 76 women Comparing it to LNG-IUS)	No direct evidence with comparator	−76.93 (−153.82 to −0.05)	**Mean blood loss with long-cycle progestogen was** **76.93 lower (153.82 to 0.05 lower) than placebo**	⊕⊕⊖⊖ Low[d,e]	4.1 (SUCRA 70%)
LNG-IUS	No direct evidence with comparator	−105.71 (−201.10 to −10.33)	**Mean blood loss with LNG-IUS was 105.7 lower** **(201.1 to 10.3 lower) than placebo**	⊕⊕⊖⊖ Low[d,e]	2.4 (SUCRA 80%)
Ethamsylate	No direct evidence with comparator	10.20 (−73.73 to 94.12)	Mean blood loss with ethamsylate 10.2 higher (73.73 lower to 94.12 higher) than placebo	⊕⊖⊖⊖ Very low[e,g]	8.9 (SUCRA 10%)
Placebo	Reference comparator	Not estimable	Not estimable	Reference comparator	8.9 (SUCRA 10%)

CI: confidence interval; **NMA**: network meta-analysis.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Estimates are reported as mean difference.
[b]Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).
[c]Danazol: despite being effective in reducing menstrual bleeding, its adverse events advise against its use for HMB. Included in the NMA to provide indirect evidence. Danazol results are not included in the summary of findings.
[d]Downgraded one level for serious risk of bias of direct evidence.
[e]Downgraded one level for serious imprecision.
[f]Downgraded two levels for very serious imprecision.
[g]Downgraded 2 levels for very serious risk of bias of direct evidence.

Table 6. Summary of findings for first-line treatments: mean blood loss (sensitivity analysis)

Estimated effects, confidence intervals, and certainty of the evidence for menstrual bleeding reduction Mean blood loss at the end of treatment with first-line treatment

BENEFITS

Patient or population: women with heavy menstrual bleeding

Interventions: non-steroidal anti-inflammatory drugs (NSAIDs), antifibrinolytics, combined oral contraceptive (COC), combined vaginal ring (CVR), luteal cyclical progestogen (luteal Pg), long-cycle progestogen (long-cycle Pg), levonorgestrel intrauterine system (LNG-IUS **),** danazol and ethamsylate

Comparator (reference): placebo

Outcome: menstrual bleeding reduction (PBAC reduction)

Setting: Clinical

Network geometry plot: Figure 7

Total studies: 23 trials, 1193 women with direct evidence for all comparisons. 8 trials with 710 women compared the Interventions versus placebo.

Intervention	N trials and N women (direct evidence with comparator)	Relative effect[a] (95% CI) (from network)	Mean difference	Certainty of evidence	Mean rank (1 to 10) and SUCRA[b]
NSAIDs Other direct evidence 5 trials, 215 women Comparing NSAIDs to ethamsylate, antifibrinolytics, luteal progestogen and danazol[c]	5 trials, 145 women	**−45.81** **(−78.83 to −12.80)**	**Mean blood loss with NSAIDs 138.19 45.81 lower** **(78.83 to 12.80 lower) than placebo**	⊕⊖⊖⊖ Very low[d,e,f]	6.9 (SUCRA 30%)
Antifibrinolytics Other direct evidence 4 trials, 358 women Comparing antifibrinolytics to luteal and long-cycle progestogens	2 trials, 84 women	**−107.93** **(−155.12 to −60.73)**	**Mean blood loss with antifibrinolytics 107.93 lower** **(155.12 to 60.73 lower) than placebo**	⊕⊖⊖⊖ Very low[d,e,f,g]	3.1 (SUCRA 80%)
COC Other direct evidence 3 trials, 170 women Comparing COC to CVR, LNG-IUS and danazol[c]	No direct evidence with comparator	−48.48 (−111.89 to 14.93)	Mean blood loss with COC 48.48 lower (111.89 lower to 14.93 higher) than placebo	⊕⊖⊖⊖ Very low[d,e,f]	6.9 (SUCRA 30%)
CVR Other direct evidence 1 trial, 95 women	No direct evidence with comparator	**−87.04** **(−157.23 to −16.86)**	**Mean blood loss with CVR 87.04 lower** **(157.23 to 16.86 lower) than placebo**	⊕⊖⊖⊖ Very low[d,e,f]	4.4 (SUCRA 60%)

Table 6. Summary of findings for first-line treatments: mean blood loss (sensitivity analysis) *(Continued)*

Comparing CVR to long-cycle progestogen

Luteal Pg Other direct evidence 2 trials, 50 women Comparing it to danazol[c]	No direct evidence with comparator	−39.17 (−92.76 to 14.41)	Mean blood loss with luteal Pg 39.17 lower (92.6 lower to 14.4 higher) than placebo	⊕⊖⊖⊖ Very low[d,e,f,g]	7.3 (SUCRA 30%)
Long-cycle Pg Other direct evidence 1 trial, 76 women Comparing to LNG-IUS	No direct evidence with comparator	**−110.32** **(−170.75 to −49.9)**	**Mean blood loss with l**ong-cycle**progestogen MD 110.32 lower (170.75 to 49.9 lower) than placebo**	⊕⊖⊖⊖ Very low[d,e,f]	3.0 (SUCRA 80%)
LNG-IUS	No direct evidence with comparator	**−175.34** **(−248.09 to −102.58)**	**Mean blood loss with LNG-IUS 175 lower** **(248 to 102 lower) than placebo**	⊕⊖⊖⊖ Very low[d,e,f]	1.0(SUCRA 100%)
Ethamsylate	No direct evidence with comparator	−2.56 (−66.84 to 61.73)	Mean blood loss with ethamsylate 2.56 lower (66.84 lower to 61.73 higher) than placebo	⊕⊖⊖⊖ Very low[d,e,f]	9.1 (SUCRA 10%)
Placebo	Reference comparator	Not estimable	Not estimable	Reference comparator	9.4 (SUCRA 10%)

CI: confidence interval; **NMA**: network meta-analysis;**PBAC**: pictorial blood assessment chart.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Estimates are reported as mean difference.
[b]Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).
[c]Danazol: despite being effective in reducing menstrual bleeding, its adverse events advise against its use for HMB. Included in the NMA to provide indirect evidence. Danazol results are not included in the summary of findings.
[d]Downgraded one level for serious risk of bias of the direct evidence.
[e]Downgraded one level for serious imprecision.
[f]Downgraded one level for network incoherence.

Table 7. Summary of findings for first-line treatments: perception of improvement

Estimated effects, confidence intervals, and certainty of the evidence for women's perception of heavy menstrual bleeding improvement with first-line treatment

BENEFITS

Patient or population: women with heavy menstrual bleeding

Interventions: Non-steroidal anti-inflammatory drugs (NSAIDs), antifibrinolytics, combined oral contraceptive (COC), combined vaginal ring (CVR), luteal cyclical progestogen (luteal Pg), long-cycle progestogen (long-cycle Pg), levonorgestrel intrauterine device (LNG-IUS**),** danazol and ethamsylate

Comparator (reference): placebo

Outcome: women's perception of heavy menstrual bleeding improvement

Setting: clinical

Network geometry plot: Figure 11

Total studies: 16, total participants: 1300 (direct evidence) for all comparisons. Interventions versus placebo: 4 RCTs, 487 women

Intervention	N trials and N women (direct evidence with comparator)	Relative effect[a] (95% CI) (from network)	Anticipated absolute effect[b](95% CI)			Certainty of evidence	Mean rank (1 to 10) and SUCRA[c]
			Without intervention (with comparator, placebo)	With intervention	Difference		
NSAIDs Other direct evidence 3 RCTs, 272 women Comparing it to ethamsylate, antifibrinolytics,and luteal progestogen)	1 RCT, 80 women	7.24 (1.19 to 44.01)	367 per 1000	808 per 1000	**441 more per 1000** (41 to 595 more)	⊕⊖⊖⊖ Very low[d,e,f]	5.3 (SUCRA 50%)
Antifibrinolytics Other direct evidence 4 RCTs, 330 women Comparing it to cyclical progestogen (luteal ad long-cycle) and LNG-IUS)	1 RCT, 68 women	11.13 (1.79 to 69.30)	367 per 1000	866 per 1000	**499 more per 1000** (142 to 609 more)	⊕⊖⊖⊖ Very low[d,e,f]	3.9 (SUCRA 70%)

Table 7. Summary of findings for first-line treatments: perception of improvement *(Continued)*

COC Other direct evidence 1 RCT, 50 women Comparing COC to CVR	2 RCTs, 339 women	5.43 (1.19 to 24.73)	367 per 1000	759 per 1000	**392 more per 1000** (41 to 568 more)	⊕⊖⊖⊖ Very low[d,e,f]	6.0 (SUCRA 40%)
CVR	No direct evidence with comparator	14.49 (0.86 to 244.30)	367 per 1000	894 per 1000	527 more per 1000 (34 fewer to 626 more)	⊕⊖⊖⊖ Very low[d,e,f]	3.8 (SUCRA 70%)
Luteal Pg Other direct evidence 2 RCTs, 54 women Comparing it to danazol[g]	No direct evidence with comparator	3.30 (0.44 to 24.68)	367 per 1000	657 per 1000	290 more per 1000 (164 fewer to 568 more)	⊕⊖⊖⊖ Very low[d,e,f]	7.6 (SUCRA 30%)
Long-cycle Pg Other direct evidence: 2 RCTs, 107 women Comparing it to LNG-IUS	No direct evidence with comparator	5.78 (0.43 to 77.71)	367 per 1000	770 per 1000	403 more per 1000 (167 fewer to 611 more)	⊕⊖⊖⊖ Very low[d,e,f]	5.9 (SUCRA 50%)
LNG-IUS	No direct evidence with comparator	20.73 (1.60 to 267.83)	367 per 1000	923 per 1000	556 more per 1000 (114 to 627 more)	⊕⊖⊖⊖ Very low[d,f,h]	2.6 (SUCRA 80%)
Ethamsylate	No direct evidence with comparator	3.84 (0.28 to 52.54)	367 per 1000	690 per 1000	323 more per 1000 (227 fewer to 601 more)	⊕⊖⊖⊖ Very low[e,f,i]	6.8 (SUCRA 40%)
Placebo	Reference comparator	Not estimable	Not estimable	Not estimable	Not estimable	Reference comparator	9.5 (SUCRA 10%)

CI: confidence interval; **NMA**: network meta-analysis.

Grade Working Group grades of evidence (or certainty of evidence)

Table 7. Summary of findings for first-line treatments: perception of improvement *(Continued)*

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

---

[a]Estimates are reported as odds ratio (OR) and Confidence interval (CI).

[b]Anticipated absolute effect. Anticipated absolute effects compares two risks by calculating the difference between the risks of the intervention groups with the risk of the control group.

[c]Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).

[d]Downgraded one level for serious risk of bias of the direct evidence.

[e]Downgraded two levels for serious imprecision.

[f]Downgraded one level for network incoherence.

[g]Danazol: despite being effective in reducing menstrual bleeding, its adverse events advise against its use for HMB. Included in the NMA to provide indirect evidence. Danazol results are not included in the summary of findings.

[h]Downgraded one level for serious imprecision.

[i]Downgraded two levels for very serious risk of bias of the direct evidence.

Table 8. Summary of findings for first-line treatments: satisfaction

Estimated effects, confidence intervals, and certainty of the evidence for satisfaction with first-line treatment

BENEFITS

Patient or population: women with heavy menstrual bleeding

Interventions: antifibrinolytics, luteal cyclical progestogen (Luteal Pg) and levonorgestrel intrauterine system (LNG-IUS)

Comparator (reference): combined oral contraceptive (COC)

Outcome: treatment satisfaction

Setting: Clinical

Direct evidence: 2 trials with 99 women; 2 three-arm studies)

Network geometry plot: Figure 15

Intervention	Relative effect[b] (95% CI) (from network)	Anticipated absolute effects[a] (95% CI)			Certainty of the evidence (GRADE) for direct evidence	Mean rank (1 to 4) and SUCRA[c]
		Without intervention (with comparator, placebo) (direct evidence with comparator)	With intervention	Difference		
Antifibrinolytics	1.05 (0.12 to 9.12)	623 per 1000	623 per 1000	12 more (452 fewer to 324 more)	⊕⊖⊖⊖ Very low[d,e]	3.1 (SUCRA 30%)
Luteal progestogen	1.40 (0.15 to 12.61)	688 per 1000	688 per 1000	76 more (420 fewer to 341 more)	⊕⊖⊖⊖ Very low[d,e]	2.6 (SUCRA 50%)
LNG-IUS	3.39 (0.72 to 16.07)	842 per 1000	842 per 1000	231 more (8 fewer to 351 more)	⊕⊖⊖⊖ Very low[e,f]	1.3 (SUCRA 90%)
COC	Reference comparator	Not estimable	Not estimable	Not estimable	Reference comparator	3.1 (SUCRA 30%)

CI: confidence interval; **NMA**: network meta-analysis.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Table 8. Summary of findings for first-line treatments: satisfaction *(Continued)*

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Anticipated absolute effect. Anticipated absolute effects compares two risks by calculating the difference between the risks of the intervention groups with the risk of the control group.
[b]Estimates are reported as odds ratio (OR) and confidence interval (CI).
[c]Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).
[d]Downgraded two levels for very serious risk of bias of the direct evidence.
[e]Downgraded two levels for very serious imprecision.
[f]Downgraded one level for serious risk of bias of the direct evidence.

Table 9. Summary of findings for first-line treatments: quality of life

Intervention	Comparator	Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	№ of women (trials)	Certainty of the evidence (GRADE)
			Risk with comparator	Risk with intervention			
Antifibrinolytics	Long-cycle progestogen	Quality of life (SF-36 general health)	There was no clear evidence of difference when comparing long-cycle progestogen with antifibrinolytics (MD 5.00, 95% CI −2 to 12)		—	90 women (1 RCT)	⊕⊕⊖⊖ Low[b]
	Short-cycle progestogen	Quality of life (proportion reporting improvement)	300 per 1000 women reported improvement in quality of life with short-cycle progestogen	501 per 1000 women (228 to 1000 women) reported improvement in quality of life with antifibrinolytics	RR 1.67 (0.76 to 3.64)	44 women (1 RCT)	⊕⊖⊖⊖ Very low[c,d]
LNG-IUS	Combined oral contraceptive	Quality of life (good or excellent)	235 per 1,000 women reported good or excellent quality of life with COC	282 per 1,000 women (169 to 471 women) reported good or excellent quality of life with	RR 1.20 (0.72 to 2.00)	170 (2 RCTs)	⊕⊕⊖⊖ Low[c,e]

CI: confidence interval; **MD**: mean difference; **RCT**: randomised controlled trial; **RR**: relative risk

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[b]Downgraded two levels for very serious risk of bias.
[c]Downgraded one level for serious risk of bias.
[d]Downgraded two levels for imprecision.
[e]Downgraded one level for imprecision.

Table 10. Summary of findings for first-line treatments: any adverse event

Estimated effects, confidence intervals, and certainty of the evidence for any adverse events with medical treatments for heavy menstrual bleeding (HMB) with first-line treatment

BENEFITS

Patient or population: women with heavy menstrual bleeding

Interventions: non-steroidal anti-inflammatory drugs (NSAIDs), antifibrinolytics, combined oral contraceptive (COC), luteal cyclical progestogen (luteal Pg), long-cycle progestogen (long-cycle Pg), levonorgestrel intrauterine system (LNG-IUS**) and** danazol

Comparator (reference): placebo

Outcome: any adverse event

Setting: clinical

Network geometry plot: Figure 19

Total studies: 14 trials, 1341 women with direct evidence for all comparisons. Three trials with 643 women compared the interventions versus placebo

Intervention	N trials and N women (direct evidence with comparator)	Relative effect[a] (95% CI) (from network)	Anticipated absolute effect[b] (95% CI)			Certainty of evidence	Mean rank (1 to 8) and SUCRA[c]
			Without intervention (with comparator, placebo)	With intervention	Difference		
NSAIDs Other direct evidence 2 trials, 143 women Comparing NSAIDs antifibrinolytics and luteal progestogen	Only indirect evidence	1.14 (0.24 to 5.48)	505 per 1000	537 per 1000	32 more (308 fewer to 343 more)	⊕⊕⊝⊝ Low[d,e]	2.8 (SUCRA 70%)
Antifibrinolytics Other direct evidence 5 trials, 415 women Comparing antifibrinolytics to luteal, long-cycle progestogens and LNG-IUS	1 trial, 297 women	1.29 (0.63 to 2.63)	505 per 1000	568 per 1000	63 more (114 fewer to 224 more)	⊕⊕⊝⊝ Low[d,e]	2.7 (SUCRA 80%)
COC	2 trials,	2.21	505 per 1000	692 per 1000	**188 more**	⊕⊕⊝⊝	5.2

Table 10. Summary of findings for first-line treatments: any adverse event *(Continued)*

Other direct evidence 1 trial, 39 women Comparing COC to LNG-IUS	346 women	(1.43 to 3.41)			**(88 to 272 more)**	Low[f]	(SUCRA 40%)
Luteal Pg Other direct evidence 3 trials, 101 women Comparing luteal progestogen to danazol[g]	No direct evidence with comparator	2.10 (0.82 to 5.38)	505 per 1000	681 per 1000	177 more (49 fewer to 341 more)	⊕⊖⊖⊖ Very low[f,h]	5.0 (SUCRA 40%)
Long-cycle Pg	No direct evidence with comparator	2.62 (0.96 to 7.17)	505 per 1000	727 per 1000	223 more (10 fewer to 375 more)	⊕⊖⊖⊖ Very low[d,f]	5.8 (SUCRA 30%)
LNG-IUS	No direct evidence with comparator	2.10 (0.69 to 6.38)	505 per 1000	681 per 1000	177 more (92 fewer to 362 more)	⊕⊕⊖⊖ Low[d,e]	4.9 (SUCRA 40%)
Placebo	Reference comparator	Not estimable	Not estimable	Not estimable	Not estimable	Reference comparator	1.9 (SUCRA 90%)

CI: confidence interval; **NMA**: network meta-analysis.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Estimates are reported as odds ratio (OR) and confidence interval (CI).
[b]Anticipated absolute effect. Anticipated absolute effects compares two risks by calculating the difference between the risks of the intervention groups with the risk of the control group.

[c]Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).
[d]Downgraded one level for serious risk of bias of the direct evidence.
[e]Downgraded one level for serious imprecision.
[f]Downgraded two levels for very serious imprecision.
[g]Danazol: despite being effective in reducing menstrual bleeding, its adverse events advise against its use for HMB. Included in the NMA to provide indirect evidence. Danazol results are not included in the summary of findings.
[h]Downgraded two levels for very serious risk of bias of the direct evidence.

Table 11. Summary of findings for first-line treatments: serious adverse events

Interventions compared with placebo or no treatment

Intervention	Comparator	Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	N women (trials)	Certainty of the evidence (GRADE)
			Risk with placebo	Risk with antifibrinolytics			
Antifibrinolytics	Placebo	Serious adverse events	7 per 1000 women experienced a serious adverse event with placebo	1 per 1000 women (range 1 to 35 women) experienced a serious adverse event with antifibrinolytics	RR 0.10 (0.00 to 2.46	468 (2 RCTs)	⊕⊕⊕⊖ Moderate[b]

CI: confidence interval; **RCT**: randomised controlled trial; **RR**: relative risk.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[b]Downgraded one level for serious risk of bias.

Table 12. Summary of findings for first-line treatments: requirement for further treatment

Interventions compared with placebo or no treatment

Intervention	Comparator	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	N women (trials)	Certainty of the evidence (GRADE)
		Risk with comparator	Risk with intervention			
LNG-IUS	Combined oral contraceptives	254 per 1000 women with combined oral contraceptives experienced treatment failure or required further treatment	109 per 1000 (61 to 201) women with LNG-IUS experienced treatment failure or required further treatment	**RR 0.43** **(0.24 to 0.79)**	208 (2 RCTs)	⊕⊕⊖⊖ Low[b,c]

CI: confidence interval; **RCT**: randomised controlled trial; **RR**: relative risk.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[b]Downgraded one level for serious risk of bias.
[c]Downgraded one level for imprecision.

Table 13. Summary of findings for second-line treatments: bleeding (pictorial blood assessment chart) improvement (no imputed data)

Estimated effects, confidence intervals, and certainty of the evidence for bleeding improvement (PBAC) with second-line treatment for heavy menstrual bleeding (no imputed data)

BENEFITS

Patient or population: women with HMB, surgical candidates (with medical treatment failure, have completed their families or hysterectomy candidates)

Interventions: resectoscopic endometrial ablation (REA), non-resectoscopic endometrial ablation (NREA) and hysterectomy[a] (all routes of hysterectomy)

Comparator (reference): LNG-IUS

Outcome: bleeding improvement (without inputted data)

Setting: clinical

Network geometry plot: Figure 74

Total studies: 11 trials, 1790 women with direct evidence for all comparisons. Six trials with 508 women comparing interventions versus LNG-IUS (comparator)

Intervention	N trials and N women (direct evidence with comparator)	Relative effect[b] (95% CI) (from network)	Anticipated absolute effect[c] (95% CI)			Certainty of evidence	Mean rank (1 to 4) and SUCRA[d]
			Without intervention (with comparator, LNG-IUS)	With intervention	Difference		
NREA Other direct evidence 5 trials, 1282 women Comparing NREA to REA	2 trials, 104 women	3.32 (1.53 to 7.23)	822 per 1000	939 per 1000	**117 more** (54 to 149 more)	⊕⊕⊕⊖ Moderate[e]	2.0 (SUCRA 70%)
REA	3 trials, 179 women	2.70 (1.29 to 5.66)	822 per 1000	926 per 1000	**104 more** (34 to 141 more)	⊕⊕⊖⊖ Low[f]	2.8 (SUCRA 40%)
Hysterectomy[a]	1 trial, 225 women.	25.71 (1.50 to 439.96)	822 per 1000	992 per 1000	**169 more** (52 to 177 more)	⊕⊕⊖⊖ Low[g]	1.2 (SUCRA 90%)
LNG-IUS	Reference	Not estimable	Not estimable	Not estimable	Not estimable	Reference	4.0

Table 13. Summary of findings for second-line treatments: bleeding (pictorial blood assessment chart) improvement (no imputed data) *(Continued)*

	comparator		comparator	(SUCRA 0%)

CI: confidence interval; **HMB**: heavy menstrual bleeding; **PBAC**: pictorial blood assessment chart.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]As bleeding control and requirement of further surgery for HMB are related to total or subtotal hysterectomy and to to the route of the hysterectomy, in this case all hysterectomies are grouped as one intervention.
[b]Estimates are reported as odds ratios (OR) and confidence interval (CI).
[c]Anticipated absolute effect. Anticipated absolute effects compares two risks by calculating the difference between the risks of the intervention groups with the risk of the control group.
[d]Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).
[e]Downgraded one level for serious risk of bias of the direct evidence.
[f]Downgraded two levels for very serious risk of bias of the direct evidence.
[g]Downgraded one level for serious imprecision.

Table 14. Summary of findings for second-line treatments: bleeding improvement (with imputed data)

Estimated effects**, confidence intervals, and certainty of the evidence for bleeding improvement (PBAC) with second-line treatment for heavy menstrual bleeding (with imputed data)**

BENEFITS

Patient or population: women with HMB, surgical candidates (with medical treatment failure, have completed their families or hysterectomy candidates)

Interventions: resectoscopic endometrial ablation (REA), non-resectoscopic**endometrial ablation (NREA) and hysterectomy* (all routes of hysterectomy)**

Comparator (reference): LNG-IUS

Outcome: bleeding improvement (with inputted data)

Setting: clinical

Network geometry plot: Figure 27

Table 14. Summary of findings for second-line treatments: bleeding improvement (with imputed data) *(Continued)*

Total studies: 15 trials, 2241 women with direct evidence for all comparisons. 7 trials with 582 women compared one intervention versus LNG-IUS

Intervention	N trials and N women (direct evidence with comparator)	Relative effect[a] (95% CI) (from network)	Anticipated absolute effect[b] (95% CI)			Certainty of evidence	Mean rank (1 to 4) and SUCRA[c]
			Without intervention (with comparator, LNG-IUS)	With intervention	Difference		
NREA Other direct evidence 7 trials, 1591 women Comparing NREA to REA	2 trials, 104 women	2.87 (1.29 to 6.05)	838 per 1000	937 per 1000	**99 more** (33 to 131 more)	⊕⊕⊕⊖ Moderate[d]	2.2 (SUCRA 60%)
REA	3 trials, 179 women	2.65 (1.29 to 5.45)	838 per 1000	932 per 1000	**94 more** (32 to 128 more)	⊕⊖⊖⊖ Very low[e,f]	2.7 (SUCRA 40%)
Hysterectomy[g] Other direct evidence 1 trial, 68 women Comparing hysterectomy and NREA	2 trials, 299 women	14.31 (2.99 to 68.56)	838 per 1000	987 per 1000	**149 more** (101 to 159 more)	⊕⊕⊖⊖ Low[d,f]	1.0 (SUCRA 100%)
LNG-IUS	Reference comparator	Not estimable	Not estimable	Not estimable	Not estimable	Reference comparator	4.0 (SUCRA 0%)

CI: confidence interval; **HMB**: heavy menstrual bleeding; **PBAC**: pictorial blood assessment chart.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Table 14. Summary of findings for second-line treatments: bleeding improvement (with imputed data) *(Continued)*

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Estimates are reported as odds ratio (OR) and Confidence interval (CI).
[b]Anticipated absolute effect. Anticipated absolute effects compares two risks by calculating the difference between the risks of the intervention groups with the risk of the control group.
[c]Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).
[d]Downgraded one level for serious risk of bias of the direct evidence.
[e]Downgraded two levels for very serious risk of bias of the direct evidence.
[f]Downgraded one level for serious imprecision.
[g]As bleeding control and requirement of further surgery for HMB are related to total or subtotal hysterectomy and to to the route of the hysterectomy, in this case all hysterectomies are grouped as one intervention.

Table 15. Summary of findings for second-line treatments: amenorrhoea

Estimated effects**, confidence intervals, and certainty of the evidence for amenorrhoea with second-line treatment for heavy menstrual bleeding**

BENEFITS

Patient or population: women with HMB, surgical candidates (with medical treatment failure, have completed their families or hysterectomy candidates)

Interventions: resectoscopic endometrial ablation (REA), non-resectoscopic**endometrial ablation (NREA) and hysterectomy[a] (all routes of hysterectomy)**

Comparator (reference): LNG-IUS

Outcome: amenorrhoea

Setting: clinical

Network geometry plot: Figure 30

Total studies: 18 trials, 2484 women with direct evidence for all comparisons. Six trials with 329 women compared the interventions versus LNG-IUS (comparator)

Intervention	N trials and N women (direct evidence with comparator)	Relative effect[b] (95% CI) (from network)	Anticipated absolute effect[c] (95% CI)			Certainty of evidence	Mean rank (1 to 4) and SUCRA[d]
			Without intervention (with comparator, LNG-IUS)	With intervention	Difference		
NREA	2 trials,	1.14	595 per 1000	626 per 1000	31 more	⊕⊖⊖⊖	2.9

Table 15. Summary of findings for second-line treatments: amenorrhoea *(Continued)*

Other direct evidence 12 trials, 2155 women Comparing NREA to REA	83 women	(0.57 to 2.29)			(139 fewer to 176 more)	Very low[e,f,g]	(SUCRA 40%)
REA	3 trials, 169 women	1.16 (0.58 to 2.31)	595 per 1000	630 per 1000	35 more (135 fewer to 178 more)	⊕⊖⊖⊖ Very low[f,h]	2.8 (SUCRA 40%)
Hysterectomy[h]	1 trial, 77 women	62.11 (3.57 to 1079.05)	595 per 1000	989 per 1000	**394 more** (251 to 404 more)	⊕⊖⊖⊖ Very low[h,j]	1.0 (SUCRA 100%)
LNG-IUS	Reference comparator	Not estimable	Not estimable	Not estimable	Not estimable	Reference comparator	3.3 (SUCRA 20%)

CI: confidence interval; **HMB**: heavy menstrual bleeding.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]As bleeding control and requirement of further surgery for HMB are related to total or subtotal hysterectomy and to to the route of the hysterectomy, in this case all hysterectomies are grouped as one intervention.
[b]Estimates are reported as odds ratio (OR) and confidence interval (CI).
[c]Anticipated absolute effect. Anticipated absolute effects compares two risks by calculating the difference between the risks of the intervention groups with the risk of the control group.
[d] Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).
[e]Downgraded one level for serious risk of bias of the direct evidence.
[f]Downgraded two levels for very serious risk of bias of the direct evidence.
[i]Downgraded one level for serious imprecision (wide intervals).

[g]Downgraded one level for high heterogeneity on the direct evidence.
[h]As bleeding control and requirement of further surgery for HMB are related to total or subtotal hysterectomy and to to the route of the hysterectomy, in this case all hysterectomies are grouped as one intervention.
[j]Downgraded two levels for very serious imprecision.

Table 16. Summary of findings for second-line treatments: satisfaction

Estimated effects**, confidence intervals, and certainty of the evidence for satisfaction with second-line treatment for heavy menstrual bleeding**

BENEFITS

Patient or population: women with HMB, surgical candidates (with medical treatment failure, have completed their families or hysterectomy candidates)

Interventions: resectoscopic endometrial ablation (REA), non-resectoscopic**endometrial ablation (NREA), non specified endometrial ablation (EA), levonorgestrel releasing intrauterine device (LNG-IUS), minimally invasive hysterectomy and open hysterectomy**

Comparator (reference): LNG-IUS

Outcome: satisfaction

Setting: clinical

Network geometry plot: Figure 34

Total studies: 27 trials, 4284 women with direct evidence for all comparisons; 9 trials with 981 women compared the interventions versus **hysterectomy (any/unspecified route), the comparator**

Intervention	N trials and N women (direct evidence with comparator)	Relative effect[a] (95% CI) (from network)	Anticipated absolute effect[c] (95% CI)			Certainty of evidence	Mean rank (1 to 7) and SUCRA [d]
			Without intervention (with the comparator)	With intervention	Difference		
NREA Other direct evidence 14 trials, 2591 women Comparing NREA to REA and minimally invasive hysterectomy)	6 trials, 622 women	1.59 (1.09 to 2.33)	792 per 1000	859 per 1000	**67 more** (15 to 107 more)	⊕⊕⊖⊖ Low[d]	3.6 SUCRA 60%
REA Other direct evidence 2 trials, 313 women	2 trials, 127 women	1.25 (0.80 to 1.96)	792 per 1000	827 per 1000	34 more (39 fewer to 9 more)	⊕⊖⊖⊖ Very low[d,e]	5.0 SUCRA 30%

Table 16. Summary of findings for second-line treatments: satisfaction *(Continued)*

Comparing REA to hysterectomy (any/unspecified) and open hysterectomy

EA (unspecified) Other direct evidence 2 trials, 399 women Comparing EA (unspecified) to hysterectomy (any/unspecified)	No direct evidence with comparator	1.00 (0.36 to 2.78)	792 per 1000	792 per 1000	0 fewer (214 fewer to 122 more)	⊕⊖⊖⊖ Very low[f,g]	5.8 SUCRA 20%
Hysterectomy (any/unspecified route)	1 trial, 232 women	1.34 (0.56 to 3.21)	792 per 1000	836 per 1000	44 more (111 fewer to132 more)	⊕⊖⊖⊖ Very low[f,g]	4.4 SUCRA 40%
Minimally invasive hysterectomy	No direct evidence with comparator	7.96 (3.33 to 19.03)	792 per 1000	968 per 1000	**176 more** (135 more to 194 more)	⊕⊕⊖⊖ Low[d]	1.3 SUCRA 100%
Open hysterectomy	No direct evidence with comparator	5.13 (1.32 to 19.92)	792 per 1000	951 per 1000	**158 more** (42 to 195 more)	⊕⊖⊖⊖ Very low[d,e]	1.8 SUCRA 90%
LNG-IUS	Reference comparator	Not estimable	Not estimable	Not estimable	Not estimable	Reference comparator	6.1 SUCRA 20%

CI: confidence interval; **HMB**: heavy menstrual bleeding.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Estimates are reported as odds ratio (OR) and confidence interval (CI).
[b]Anticipated absolute effect. Anticipated absolute effects compares two risks by calculating the difference between the risks of the intervention groups with the risk of the control group.

[c]Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).
[d]Downgraded two levels for very serious risk of bias of the direct evidence.
[e]Downgraded one level for serious imprecision.
[f]Downgraded one level for serious risk of bias of the direct evidence.
[g]Downgraded two levels for very serious imprecision

Table 17. Summary of findings for second-line treatments: quality of life

Intervention	Comparator	Outcome	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	N trials (participants)	Certainty of the evidence (GRADE)
			Risk with comparator	Risk with intervention			
NREA	LNG-IUS	SF-36 general health	There may be little to no difference between NREA and LNG-IUS (MD 2.9, 95% CI −3.10 to 9.02)		—	2 trials 98 women	⊕⊕⊖⊖ Low[b,c]
	Minimally invasive hysterectomy	SF-36 general health	Women with minimally invasive hysterectomy may be more likely to have a better quality of life up to two years follow-up than women with NREA (MD −10.90, 95% CI −15.81 to −5.99)		—	1 trial 68 participants	⊕⊕⊖⊖ Low[d]
		Proportion with MMAS = 100	583 per 1000 women in the minimally invasive group	478 per 1000 women in the NREA group	RR 0.82 (0.70 to 0.95)	1 trial 616 participants	⊕⊕⊕⊖ Moderate[b]
REA	Minimally invasive hysterectomy	SF-36 general health	There may be little to no difference between REA and minimally invasive hysterectomy (MD −9.90, 95% CI −19.89 to 0.09)		—	1 trial 67 participants	⊕⊕⊖⊖ Very low[b,d]
	Open hysterectomy	SF-36 general health	There may be little to no difference between REA and open hysterectomy (MD −5.30, 95% CI −11.90 to 1.30)		—	1 trial 155 women	⊕⊕⊖⊖ Very low[b,d]
EA unspecified	Hysterectomy (unspecified)	SF-36 general health	There may be little to no difference between EA (unspecified) and hysterectomy (unspecified route) (MD −1.90, 95% CI −8.67 to 4.87)		—	1 trial 204 women	⊕⊕⊖⊖ Very low[b,d]

Table 17. Summary of findings for second-line treatments: quality of life *(Continued)*

LNG-IUS	Minimally invasive hysterectomy	SF-36 general health	There may be little to no difference between LNG-IUS and minimally invasive hysterectomy (MD −1.50 points, 95% CI −4.28 to 1.28)	—	1 trial 72 women	⊕⊕⊖⊖ Very low[b,d]
	Hysterectomy (unspecified)	SF-36 general health	There may be little to no difference between LNG-IUS and hysterectomy (unspecified route) (MD 2.20, 95% CI −2.93 to 7.33)	—	1 trial 221 women	⊕⊕⊖⊖ Very low[b,c]

CI: confidence interval; **EA**: endometrial ablation; **LNG-IUS**: levonorgestrel releasing intrauterine device; **MD**: mean difference; **MMAS**: Menorrhagia Multiatribute Scale (100 = best possible result); **NREA**: non-resectoscopic endometrial ablation; **RCT**: randomised controlled trial; **REA**: resectoscopic endometrial ablation; **RR**: relative risk; **SF-36**: Short Form Health Survey.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[b]Downgraded one level for serious risk of bias.
[c]Downgraded one level for imprecision.
[d]Downgraded two levels for imprecision.

Table 18. Summary of findings for second-line treatments: any adverse event

Estimated effects**, confidence intervals, and certainty of the evidence for any adverse event with second-line treatment for heavy menstrual bleeding**

BENEFITS

Patient or population: women with HMB, surgical candidates (with medical treatment failure, have completed their families or hysterectomy candidates)

Interventions: non-resectoscopic**endometrial ablation (NREA), resectoscopic endometrial ablation (REA), EA (unspecified), hysterectomy (any/unspecified), minimally invasive hysterectomy and open hysterectomy.**

Comparator (reference): LNG-IUS

Outcome: any adverse event

Table 18. Summary of findings for second-line treatments: any adverse event *(Continued)*

Setting: clinical

Network geometry plot: Figure 38

Total studies: 12 trials, 1878 women with direct evidence for all comparisons; 3 trials with 201 women comparing interventions versus LNG-IUS (comparator)

Intervention	N trials and N women (direct evidence with comparator)	Relative effect[a] (95% CI) (from network)	Anticipated absolute effect[b] (95% CI)			Certainty of evidence	Mean rank (1 to 6) and SUCRA[c]
			Without intervention (with comparator, LNG-IUS)	With intervention	Difference		
NREA Other direct evidence 4 trials, 967 women Comparing NREA to REA and minimally invasive hysterectomy	1 trial, 72 women	0.28 (0.11 to 0.69)	570 per 1000	271 per 1000	**299 fewer** (443 fewer to 92 fewer)	⊕⊖⊖⊖ Very low[d,e]	2.9 (SUCRA 70%)
REA Other direct evidence 4 trials, 508 women Comparing REA to minimally invasive, open and any/ unspecified hysterectomy	2 trials, 129 women	0.29 (0.15 to 0.59)	570 per 1000	285 per 1000	**285 fewer** (404 fewer to 131 fewer)	⊕⊖⊖⊖ Very low[e,f]	3.2 (SUCRA 60%)
EA (unspecified) Other direct evidence one trial, 202 women Comparing EA unspecified to hysterectomy any/unspecified	No direct evidence with comparator	0.23 (0.01 to 4.00)	570 per 1000	234 per 1000	336 fewer (557 fewer to 271 more)	⊕⊖⊖⊖ Very low[e,f]	3.0 (SUCRA 70%)
Hysterectomy (any/unspecified)	No direct evidence with comparator	1.30 (0.20 to 8.37)	570 per 1000	633 per 1000	63 more 36 fewer to 347 more)	⊕⊖⊖⊖ Very low[d,e]	6.2 (SUCRA 10%)

Table 18. Summary of findings for second-line treatments: any adverse event *(Continued)*

Minimally invasive hysterectomy	No direct evidence with comparator	0.36 (0.11 to 1.16)	570 per 1000	323 per 1000	247 fewer (443 fewer to 36 more)	⊕⊖⊖⊖ Very low[d,e]	3.9 (SUCRA 50%)
Open hysterectomy	No direct evidence with comparator	0.21 (0.30 to 1.41)	570 per 1000	218 per 1000	352 fewer (285 fewer to 81 more)	⊕⊖⊖⊖ Very low[d,e]	2.6 (SUCRA 70%)
LNG-IUS	Reference comparator	Not estimable	Not estimable	Not estimable	Not estimable	Reference comparator	6.1 (SUCRA 10%)

CI: confidence interval; **HMB**: heavy menstrual bleeding.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Estimates are reported as odds ratio (OR) and confidence interval (CI).
[b]Anticipated absolute effect. Anticipated absolute effects compares two risks by calculating the difference between the risks of the intervention groups with the risk of the control group.
[c]Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).
[d]Downgraded one level for serious risk of bias of the direct evidence.
[e]Downgraded two levels for very serious imprecision.
[f]Downgraded two levels for very serious risk of bias of the direct evidence.

Table 19. Summary of findings for second-line treatments: requirement of further surgery

Estimated effects**, confidence intervals, and certainty of the evidence for requirement of further surgery (ablation or hysterectomy) with second-line treatment for heavy menstrual bleeding**

BENEFITS

Table 19. Summary of findings for second-line treatments: requirement of further surgery *(Continued)*

Patient or population: women with HMB, surgical candidates (with medical treatment failure, have completed their families or hysterectomy candidates)

Interventions: resectoscopic endometrial ablation (REA), non-resectoscopic**endometrial ablation (NREA), endometrial ablation (any/unspecified) and hysterectomy[a] (all routes of hysterectomy)**

Comparator (reference): LNG-IUS

Outcome: r**equirement of further surgery (ablation or hysterectomy)**

Setting: clinical

Network geometry plot: Figure 42

Total studies: 22 trials, 2859 women with direct evidence for all comparisons; 8 trials with 515 women compared the interventions versus LNG-IUS the comparator

Intervention	N trials and N women (direct evidence with comparator)	Relative effect[b] (95% CI) (from network)	Anticipated absolute effect[c] (95% CI)			Certainty of evidence	Mean rank (1 to 5) and SUCRA[d]
			Without intervention (with comparator, LNG-IUS)	With intervention	Difference		
NREA Other direct evidence. 8 trials, 1389 women Comparing NREA to REA and hysterectomy[a]	3 trials, 214 women	0.52 (0.28 to 0.97)	149 per 1000	83 per 1000	**66 fewer** (102 to 4 fewer)	⊕⊕⊕⊖ Moderate[e]	2.3 (SUCRA 70%)
REA Other direct evidence 5 trials, 695 women Comparing REA to hysterectomy[a]	5 trials, 301 women	0.61 (0.32 to 1.15)	149 per 1000	96 per 1000	53 fewer (96 fewer to 19 more)	⊕⊖⊖⊖ Very low[f,g]	3.0 (SUCRA 30%)
EA (unspecified) Other direct evidence 1 trial, 260 women Comparing EA (unspecified) to hysterectomy[a]	No direct evidence with comparator	3.42 (0.14 to 78.19)	149 per 1000	374 per 1000	225 more (125 fewer to 783 more)	⊕⊖⊖⊖ Very low[e-h]	4.5 (SUCRA 10%)

Table 19. Summary of findings for second-line treatments: requirement of further surgery *(Continued)*

Hysterectomy[a]	No direct evidence with comparator	0.03 (0.01 to 0.13)	149 per 1000	5 per 1000	**144 fewer** (147 to 127 fewer)	⊕⊕⊕⊖ Moderate[f]	1.0 (SUCRA 100%)
LNG-IUS	Reference comparator	Not estimable	Not estimable	Not estimable	Not estimable	Reference comparator	4.1 (SUCRA 20%)

CI: confidence interval; **HMB**: heavy menstrual bleeding.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]As bleeding control and requirement of further surgery for HMB are related to total or subtotal hysterectomy and to to the route of the hysterectomy, in this case all hysterectomies are grouped as one intervention.
[b]Estimates are reported as odds ratio (OR) and confidence interval (CI).
[c]Anticipated absolute effect. Anticipated absolute effects compares two risks by calculating the difference between the risks of the intervention groups with the risk of the control group.
[d]Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).
[e]Downgraded one level for serious imprecision.
[f]Downgraded one level for serious risk of bias of the direct evidence.
[g]Downgraded two levels for very serious risk of bias of the direct evidence.
[h]Downgraded two levels for very serious risk of imprecision.

Table 20. Summary of findings for endometrial ablation subgroup: bleeding (pictorial blood assessment chart) improvement

Estimated effects**, confidence intervals, and certainty of the evidence for bleeding (PBAC) improvement with endometrial ablation for heavy menstrual bleeding**

BENEFITS

Table 20. Summary of findings for endometrial ablation subgroup: bleeding (pictorial blood assessment chart) improvement *(Continued)*

Patient or population: women with HMB, surgical candidates (with medical treatment failure, have completed their families or hysterectomy candidates)

Interventions: TCRE/rollerball, other resectoscopic endometrial ablation (other REA), microwave non-resectoscopic**endometrial ablation (NREA), hydrothermal ablation NREA, bipolar NREA, balloon NREA and other NREA**

Comparator (reference): TCRE/rollerball

Outcome: bleeding (PBAC) improvement

Setting: clinical

Network geometry plot: Figure 46

Total studies: 10 trials, 1852 women with direct evidence for all comparisons; 7 trials with 1602 women compared the interventions versus TCRE/rollerball (the comparator)

Intervention	N trials and N women (direct evidence with comparator)	Relative effect[a] (95% CI) (from network)	Anticipated absolute effect[b] (95% CI)			Certainty of evidence	Mean rank (1 to 7) and SUCRA[c]
			Without intervention (with comparator, TCRE/rollerball)	With intervention	Difference		
Other REA Other direct evidence 1 trial, 70 women Comparing other REA with balloon NREA	1 trial, 91 women	1.24 (0.43 to 3.61)	788 per 1000	822 per 1000	34 more (173 fewer to 142 more)	⊕⊖⊖⊖ Very low[d]	3.4 (SUCRA 60%)
Microwave NREA Other direct evidence 1 trial, 66 women Comparing microwave with bipolar NREA	2 trials, 562 women	1.57 (1.03 to 2.39)	788 per 1000	854 per 1000	**66 more** **(5 to 111 more)**	⊕⊕⊖⊖ Low[d,e]	2.0 (SUCRA 80%)
Hydrothermal ablation NREA	1 trial, 250 women	0.72 (0.37 to 1.41)	788 per 1000	728 per 1000	60 fewer (209 fewer to 52 more)	⊕⊖⊖⊖ Very low[d,f,g]	5.9 (SUCRA 20%)

Table 20. Summary of findings for endometrial ablation subgroup: bleeding (pictorial blood assessment chart) improvement *(Continued)*

Bipolar NREA Other direct evidence 1 trial, 104 women Comparing Bipolar end balloon NREA	1 trial, 236 women	1.33 (0.76 to 2.31)	788 per 1000	832 per 1000	44 more (49 fewer to 108 more)	⊕⊖⊖⊖ Very low[d,e,f]	2.9 (SUCRA 70%)
Balloon NREA	1 trial, 239 women	0.64 (0.39 to 1.05)	788 per 1000	704 per 1000	84 fewer (196 fewer to 8 more)	⊕⊖⊖⊖ Very low[d,g]	6.3 (SUCRA 10%)
Other NREA	1 trial, 234 women	1.51 (0.90 to 2.53)	788 per 1000	849 per 1000	61 more (18 fewer to 116 more)	⊕⊖⊖⊖ Very low[d,f,g]	3.0 (SUCRA 70%)
TCRE/rollerball	Reference comparator	Not estimable	Not estimable	Not estimable	Not estimable	Reference comparator	4.5 (SUCRA 40%)

CI: confidence interval; **HMB**: heavy menstrual bleeding; **PBAC**: pictorial blood assessment chart; **TCRE**: transcervical endometrial resection.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Estimates are reported as odds ratio (OR) and confidence interval (CI).
[b] Anticipated absolute effect. Anticipated absolute effects compares two risks by calculating the difference between the risks of the intervention groups with the risk of the control group.
[c]Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).
[d]Downgraded one level for inconsistency.
[e]Downgraded one level for serious imprecision.
[f]Downgraded one level for serious risk of bias of the direct evidence.

gDowngraded two levels for very serious risk of imprecision.

Table 21. Summary of findings for endometrial ablation subgroup: amenorrhoea

Estimated effects**, confidence intervals, and certainty of the evidence for amenorrhoea with endometrial ablation for heavy menstrual bleeding**

BENEFITS

Patient or population: women with HMB, surgical candidates (with medical treatment failure, have completed their families or hysterectomy candidates)

Interventions: TCRE/rollerball, other resectoscopic endometrial ablation (other REA), microwave non-resectoscopic**endometrial ablation (NREA), hydrothermal ablation NREA, bipolar NREA, balloon NREA and other NREA**

Comparator (reference): TCRE/rollerball

Outcome: amenorrhoea at one year follow-up

Setting: clinical

Network geometry plot: Figure 50

Total studies: 22 trials, 3403 women with direct evidence for all comparisons; 14 trials with 2507 women compared the interventions versus TCRE/rollerball (the comparator)

Intervention	N trials and N women (direct evidence with comparator)	Relative effect[a] (95% CI) (from network)	Anticipated absolute effect[b] (95% CI)			Certainty of evidence	Mean rank (1 to 7) and SUCRA[c]
			Without intervention (with TCRE/rollerball)	With intervention	Difference		
Other REA Other direct evidence 1 trial, 67 women Comparing other REA with balloon NREA	3 trials, 419 women	1.30 (0.46 to 3.69)	434 per 1000	499 per 1000	65 more (173 fewer to 303 more)	⊕⊕⊖⊖ Very low[d,e,f]	3.6 (SUCRA 60%)
Microwave NREA Other direct evidence 2 trials, 348 women Comparing microwave NREA with balloon and bipolar NREA	2 trials, 562 women	1.84 (0.69 to 4.93)	434 per 1000	585 per 1000	151 more (88 fewer to 357 more)	⊕⊖⊖⊖ Very low[e,f]	2.3 (SUCRA 80%)
Hydrothermal ablation NREA Other direct evidence 1 trial, 146 women	1 trial, 250 women	0.66 (0.17 to 2.56)	434 per 1000	336 per 1000	98 fewer (319 fewer to	⊕⊖⊖⊖ Very low[d,e,f]	5.6 (SUCRA 20%)

Table 21. Summary of findings for endometrial ablation subgroup: amenorrhoea *(Continued)*

Comparing hydrothermal ablation NREA and bipolar NREA					229 more)		
Bipolar NREA Other direct evidence 4 trials, 335 women Comparing bipolar to balloon NREA	2 trials, 420 women	1.86 (0.79 to 4.36)	434 per 1000	588 per 1000	154 more (57 fewer to 336 more)	⊕⊖⊖⊖ Very low[d,e,f]	2.2 (SUCRA 80%)
Balloon NREA	3 trials, 304 women	0.64 (0.28 to 1.45)	434 per 1000	329 per 1000	105 fewer (257 fewer to 92 more)	⊕⊖⊖⊖ Very low[e,f]	6.0 (SUCRA 20%)
Other NREA	3 trials, 552 women	1.11 (0.38 to 3.20)	434 per 1000	460 per 1000	32 more (208 fewer to 276 more)	⊕⊖⊖⊖ Very low[d,e,f]	4.0 (SUCRA 50%)
TCRE/rollerball	Reference comparator	Not estimable	Not estimable	Not estimable	Not estimable	Reference comparator	4.5 (SUCRA 40%)

CI: confidence interval; **HMB**: heavy menstrual bleeding; **PBAC**: pictorial blood assessment chart; **TCRE**: transcervical endometrial resection.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Estimates are reported as odds ratio (OR) and confidence interval (CI).
[b]Anticipated absolute effect. Anticipated absolute effects compares two risks by calculating the difference between the risks of the intervention groups with the risk of the control group.
[c]Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).
[d]Downgraded one level for serious risk of bias of the direct evidence.
[e]Downgraded two levels for very serious risk of imprecision.
[f]Downgraded one level for incoherence (inconsistency).

Table 22. Summary of findings for endometrial ablation subgroup: satisfaction

Estimated effects**, confidence intervals, and certainty of the evidence for satisfaction with endometrial ablation for heavy menstrual bleeding**

BENEFITS

Patient or population: women with HMB, surgical candidates (with medical treatment failure, have completed their families or hysterectomy candidates)

Interventions: o**ther resectoscopic endometrial ablation (other REA), microwave** non-resectoscopic**endometrial ablation (NREA), hydrothermal ablation NREA,** bipolar NREA**, balloon NREA and other NREA**

Comparator (reference): TCRE/r**ollerball**

Outcome: satisfaction

Setting: clinical

Network geometry plot: Figure 54

Total studies: 22 trials, 3316 women with direct evidence for all comparisons; 14 trials with 2431 women compared the interventions versus TCRE/rollerball

Intervention	N trials and N women (direct evidence with comparator)	Relative effect[a] (95% CI) (from network)	Anticipated absolute effect[b] (95% CI)			Certainty of evidence	Mean rank (1 to 7) and SUCRA[c]
			Without intervention (with TCRE/ Rollerball)	With intervention	Difference		
Other REA Other direct evidence 1 trial, 57 women Comparing other REA with balloon NREA	2 trials, 412 women	1.01 (0.53 to 1.93)	894 per 1000	895 per 1000	1 more (77 fewer to 48 more)	⊕⊕⊖⊖ Low[d,e]	4.7 (SUCRA 40%)
Microwave NREA Other direct evidence 2 trials, 346 women Comparing microwave NREA with balloon and bipolar NREA	2 trials, 533 women	1.02 (0.69 to 1.61)	894 per 1000	896 per 1000	2 more (41 fewer to 37 more)	⊕⊕⊖⊖ Low[d,e]	4.6 (SUCRA 40%)
Hydrothermal ablation NREA Other direct evidence 1 trial, 146 women	1 trial, 203 women	0.66 (0.16 to 2.64)	894 per 1000	848 per 1000	46 fewer (320 fewer to 63 more)	⊕⊖⊖⊖ Very low[d,f]	5.5 (SUCRA 20%)

Table 22. Summary of findings for endometrial ablation subgroup: satisfaction *(Continued)*

Comparing hydrothermal ablation NREA and bipolar NREA

Bipolar NREA Other direct evidence 4 trials, 336 women Comparing bipolar NREA to Balloon NREA	2 trials, 389 women	2.37 (1.39 to 4.05)	894 per 1000	952 per 1000	**58 more** (27 more to 78 more)	⊕⊕⊖⊖ Low[d,e]	1.3 (SUCRA 100%)
Balloon NREA	5 trials, 504 women	1.05 (0.67 to 1.64)	894 per 1000	898 per 1000	5 more (44 fewer to 39 more)	⊕⊕⊖⊖ Low[d,e]	4.5 (SUCRA 40%)
Other NREA	2 trials, 390 women	1.70 (0.85 to 3.40)	894 per 1000	935 per 1000	41 more (16 fewer to 72 more)	⊕⊕⊖⊖ Low[d,e]	2.3 (SUCRA 80%)
TCRE/rollerball	Reference comparator	Not estimable	Not estimable	Not estimable	Not estimable	Reference comparator	4.8 (SUCRA 40%)

CI: confidence interval; **HMB**: heavy menstrual bleeding; **PBAC**: pictorial blood assessment chart; **TCRE**: transcervical endometrial resection.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Estimates are reported as odds ratio (OR) and confidence interval (CI).
[b]Anticipated absolute effect. Anticipated absolute effects compares two risks by calculating the difference between the risks of the intervention groups with the risk of the control group.
[c]Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).
[d] Downgraded one level for serious risk of bias of the direct evidence.
[e]Downgraded one level for serious imprecision.
[f]Downgraded two levels for very serious risk of imprecision.

Table 23. Summary of findings for endometrial ablation subgroup: adverse events, perforation

Estimated effects**, confidence intervals, and certainty of the evidence for perforation with endometrial ablation for heavy menstrual bleeding**

BENEFITS

Patient or population: women with HMB, surgical candidates (with medical treatment failure, have completed their families or hysterectomy candidates)

Interventions: other resectoscopic endometrial ablation (REA), microwave non-resectoscopic**endometrial ablation (NREA), balloon NREA,** bipolar NREA**, balloon NREA and other NREA**

Comparator (reference): TCRE/r**ollerball**

Outcome: perforation

Setting: clinical

Network geometry plot: Figure 58

Total studies: 10 trials, 2421 women compared the interventions versus TCRE/rollerball; 9 trials with 2265 women compared the interventions to the comparator (TCR/rollerball)

Intervention	N trials and N women (direct evidence with comparator)	Relative effect[a] (95% CI) (from network)	Anticipated absolute effect[b] (95% CI)			Certainty of evidence	Mean rank (1 to 5) and SUCRA [d]
			Without intervention (with comparator, TCRE/rollerball)	With intervention	Difference		
Other REA	1 trial, 366 women	1.40 (0.01 to 2.71)	18 per 1000	25 per 1000	7 more (18 fewer to 29 more)	⊕⊕⊖⊖ Low[d,e]	3.0 (SUCRA 70%)
Microwave NREA	2 trials, 587 women	1.55 (0.20 to 12.12)	18 per 1000	27 per 1000	9 more (14 fewer to 162 more)	⊕⊖⊖⊖ Very low[d,f]	6.1 (SUCRA 10%)
Hydrothermal ablation	No direct evidence	0.24	18 per 1000	4 per 1000	13 fewer	⊕⊖⊖⊖ Very low[d,f]	3.9

Table 23. Summary of findings for endometrial ablation subgroup: adverse events, perforation *(Continued)*

Other direct evidence 1 trial, 156 participants Comparing it to bipolar NREA	with comparator	(0.01 to 10.38)			(18 fewer to 140 more)		(SUCRA 50%)
Bipolar NREA	1 trial, 267 women	0.07 (0.00 to 1.39)	18 per 1000	1 per 1000	13 fewer (18 fewer to 7 more)	⊕⊕⊕⊖ Moderate[d]	2.1 (SUCRA 80%)
Balloon NREA	2 trials, 382 women	0.30 (0.04 to 2.16)	18 per 1000	5 per 1000	12 fewer (17 fewer to 20 more)	⊕⊕⊖⊖ Low[d,e]	3.2 (SUCRA 60%)
Other NREA	3 trials, 663 women	0.19 (0.38 to 1.00)	18 per 1000	3 per 1000	14 fewer (11 fewer to 0 fewer)	⊕⊕⊕⊖ Moderate[d]	3.9 (SUCRA 50%)
TCRE/rollerball	Reference comparator	Not estimable	Not estimable	Not estimable	Not estimable	Reference comparator	5.8 (SUCRA 20%)

CI: confidence interval; **HMB**: heavy menstrual bleeding; **PBAC**: pictorial blood assessment chart; **TCRE**: transcervical endometrial resection.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Estimates are reported as odds ratio (OR) and confidence interval (CI).
[b]Anticipated absolute effect. Anticipated absolute effects compares two risks by calculating the difference between the risks of the intervention groups with the risk of the control group.

[c]Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).
[d]Downgraded one level for serious risk of bias of the direct evidence.
[e]Downgraded one level for serious imprecision.
[f]Downgraded two levels for very serious risk of imprecision.

Table 24. Summary of findings for endometrial ablation subgroup: further surgery (endometrial ablation or hysterectomy) for heavy menstrual bleeding

Estimated effects**, confidence intervals, and certainty of the evidence for further surgery with endometrial ablation for heavy menstrual bleeding**

BENEFITS

Patient or population: women with HMB, surgical candidates (with medical treatment failure, have completed their families or hysterectomy candidates)

Interventions: TCRE/r**ollerball, other resectoscopic endometrial ablation (other REA), microwave** non-resectoscopic**endometrial ablation (NREA), hydrothermal ablation NREA,** bipolar NREA**, balloon NREA and other NREA**

Comparator (reference): TCRE/r**ollerball**

Outcome: further (endometrial ablation or hysterectomy) surgery for HMB

Setting: clinical

Network geometry plot: Figure 62

Total studies: 13 trials, 1966 women with direct evidence for all comparisons; 7 trials with 1378 women compared the interventions versus TCRE/rollerball (the comparator)

Intervention	N trials and N women (direct evidence with comparator)	Relative effect[a] (95% CI) (from network)	Anticipated absolute effect[b] (95% CI)			Certainty of evidence	Mean rank (1 to 7) and SUCRA[c]
			Without intervention (with the comparator, TCRE/rollerball)	With intervention	Difference		
Other REA Other direct evidence 1 trial, 67 women	2 trials, 388 women	0.80 (0.49 to 1.32)	144 per 1000	119 per 1000	25 fewer (68 fewer to 38 more)	⊕⊕⊝⊝ Low[d,e]	3.5 (SUCRA 60%)

Table 24. Summary of findings for endometrial ablation subgroup: further surgery (endometrial ablation or hysterectomy) for heavy menstrual bleeding *(Continued)*

Comparing other REA with balloon NREA							
Microwave NREA	1 trial, 249 women	0.97 0.49 to 1.90)	144 per 1000	141 per 1000	4 fewer (68 fewer to 98 more)	⊕⊕⊖⊖ Low[d,e]	4.5 (SUCRA 40%)
Hydrothermal ablation NREA Other direct evidence 1 trial, 160 women Comparing hydrothermal ablation NREA and bipolar NREA	No direct evidence with comparator	2.25 (0.52 to 9.77)	144 per 1000	275 per 1000	131 more (64 fewer to 478 more)	⊕⊕⊖⊖ Low[f]	6.4 (SUCRA 10%)
Bipolar NREA Other direct evidence 4 trials, 361 women Comparing	No direct evidence with comparator	0.52 (0.19 to 1.46)	144 per 1000	81 per 1000	64 fewer (113 fewer to 53 more)	⊕⊕⊖⊖ Low[f]	2.1 (SUCRA 80%)
Balloon NREA	3 trials, 462 women	0.59 (0.31 to 1.10)	144 per 1000	91 per 1000	54 fewer (95 fewer to 12 more)	⊕⊕⊕⊖ Moderate[d]	2.2 (SUCRA 80%)
Other NREA	1 trial, 279 women	1.00 (0.42 to 2.40)	144 per 1000	144 per 1000	0 fewer (78 fewer to 144 more)	⊕⊖⊖⊖ Very low[f,g]	4.5 (SUCRA 40%)
TCRE/rollerball	Reference comparator	Not estimable	Not estimable	Not estimable	Not estimable	Reference comparator	4.8 (SUCRA 40%)

CI: confidence interval; **HMB**: heavy menstrual bleeding; **MD**: mean difference; **PBAC**: pictorial blood assessment chart; **TCRE**: transcervical endometrial resection.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Table 24. Summary of findings for endometrial ablation subgroup: further surgery (endometrial ablation or hysterectomy) for heavy menstrual bleeding *(Continued)*

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Estimates are reported as MDs.
[b]Anticipated absolute effect. Anticipated absolute effects compares two risks by calculating the difference between the risks of the intervention groups with the risk of the control group.
[c]Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).
[d]Downgraded one level for serious risk of bias of the direct evidence.
[e]Downgraded one level for serious imprecision.
[f]Downgraded two levels for very serious risk of imprecision.
[g]Downgraded two levels for very serious risk of bias of the direct evidence.

Table 25. Summary of findings for endometrial ablation subgroup: further hysterectomy for heavy menstrual bleeding

Estimated effects**, confidence intervals, and certainty of the evidence for further hysterectomy with endometrial ablation for heavy menstrual bleeding**

BENEFITS

Patient or population: women with HMB, surgical candidates (with medical treatment failure, have completed their families or hysterectomy candidates)

Interventions: microwave non-resectoscopic**endometrial ablation (NREA), hydrothermal ablation NREA,** bipolar NREA**, balloon NREA and other NREA**

Comparator (reference): TCRE/r**ollerball**

Outcome: further hysterectomy for HMB

Setting: clinical

Network geometry plot: Figure 66

Total studies: 14 trials, 2412 women with direct evidence for all comparisons. 9 trials with 1675 women compared the interventions versus TCRE/Rollerball (comparator).

Intervention	N trials and N women (direct evidence with comparator)	Relative effect[a] (95% CI)	Anticipated absolute effect[b] (95% CI)			Certainty of evidence	Mean rank (1 to 5) and SUCRA[c]
			Without intervention	With intervention	Difference		

Table 25. Summary of findings for endometrial ablation subgroup: further hysterectomy for heavy menstrual bleeding *(Continued)*

		(from network)	(with comparator)				
Microwave NREA Other direct evidence 2 trials, 353 women Comparing Microwave NREA with bipolar and balloon NREA	2 trials, 571 women	0.92 (0.49 to 1.70)	103 per 1000	95 per 1000	7 fewer (5 fewer to 6 more)	⊕⊕⊙⊙ Moderate[d]	3.9 (SUCRA 40%)
Hydrothermal ablation NREA Other direct evidence 1 trial, 160 women Comparing Hydrothermal ablation NREA with bipolar NREA	Only indirect evidence	1.39 (0.30 to 6.41)	103 per 1000	138 per 1000	35 more (70 fewer to 321 more)	⊕⊕⊙⊙ Very low[d-g]	4.9 (SUCRA 20%)
Bipolar NREA Other direct evidence 2 trials, 224 women Comparing bipolar and balloon NREA	1 trial, 153 women	0.55 (0.22 to 1.37)	103 per 1000	59 per 1000	44 fewer (78 fewer to 33 more)	⊕⊙⊙⊙ Low[d,f]	1.9 (SUCRA 80%)
Balloon NREA	3 trials, 306 women	0.86 (0.51 to 1.48)	103 per 1000	90 per 1000	13 fewer (48 fewer to 42 more)	⊕⊙⊙⊙ Low[d,f]	3.6 (SUCRA 50%)
Other REA	3 trials, 645 women	0.64 (0.33 to 1.23)	103 per 1000	68 per 1000	35 fewer (66 fewer to 21 more)	⊕⊙⊙⊙ Low[d,f]	2.3 (SUCRA 70%)
TCRE/rollerball	Reference comparator	Not estimable	Not estimable	Not estimable	Not estimable	Reference comparator	4.5 (SUCRA 30%)

CI: confidence interval; **HMB**: heavy menstrual bleeding; **MD**: mean difference; **PBAC**: pictorial blood assessment chart; **TCRE**: transcervical endometrial resection.

Grade Working Group grades of evidence (or certainty of evidence)

High certainty: we are very confident that the true lies close to that of the estimate of the effect.

Table 25. Summary of findings for endometrial ablation subgroup: further hysterectomy for heavy menstrual bleeding *(Continued)*

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

---

[a]Estimates are reported as odds ratio (OR) and confidence interval (CI).
[b]Anticipated absolute effect. Anticipated absolute effects compares two risks by calculating the difference between the risks of the intervention groups with the risk of the control group.
[c]Mean rank and SUCRA. Rank statistics is defined as the probabilities that a treatment out of N treatments in a network meta-analysis is the best, the second-best, the third-best, and so on until the least effective treatment. SUCRA (Surface Under the Cumulative RAnking curve) is a numeric presentation of the overall ranking and presents a single number associated with each treatment; SUCRA values range from 0 (worst) to 100% (best).
[d]Downgraded one level for serious risk of bias of the direct evidence.
[e]Downgraded two levels for very serious risk of bias of the direct evidence.
[f]Downgraded one level for serious imprecision.
[g]Downgraded two levels for very serious risk of imprecision.

APPENDICES

Appendix 1. Search strategy for progestin-only contraceptives for HMB

Embase

1 exp Menorrhagia/ (9472)

2 hypermenorrhea.tw. (306)

3 Menorrhagia.tw. (5205)

4 heavy menstru$.tw. (1761)

5 heavy period$.tw. (175)

6 dysfunctional uter* bleeding.tw. (1070)

7 or/1-6 (11760)

8 progestogen implant*.tw. (33)

9 (contracepti$ adj2 implant$).tw. (1384)

10 (Implanon$ or Jadelle$).tw. (1014)

11 Levonorgestrel implant$.tw. (173)

12 etonorgestrel$.tw. (50)

13 exp etonogestrel/ (2534)

14 or/8−13 (3706)

15 7 and 14 (174)

16 Clinical Trial/ (956560)

17 Randomized Controlled Trial/ (589457)

18 exp randomization/ (86255)

19 Single Blind Procedure/ (38135)

20 Double Blind Procedure/ (167151)

21 Crossover Procedure/ (62281)

22 Placebo/ (333233)

23 Randomi?ed controlled trial$.tw. (222624)

24 Rct.tw. (35951)

25 random allocation.tw. (1979)

26 randomly.tw. (431237)

27 randomly allocated.tw. (34337)

28 allocated randomly.tw. (2504)

29 (allocated adj2 random).tw. (810)

30 Single blind$.tw. (24161)

31 Double blind$.tw. (199587)

32 ((treble or triple) adj blind$).tw. (1105)

33 placebo$.tw. (297889)

34 prospective study/ (584539)

35 or/16-34 (2384555)

36 case study/ (67249)

37 case report.tw. (393966)

38 abstract report/ or letter/ (1084454)

39 or/36-38 (1535481)

40 35 not 39 (2331210)

41 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5924391)

42 40 not 41 (2169223)

43 15 and 42 (58)

Database: **Ovid MEDLINE(**R) Epub Ahead of Print, In Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily, and Ovid MEDLINE (R) 1946-Present

Search Strategy:

1 exp Menorrhagia/ (4216)

2 hypermenorrhea.tw. (245)

3 Menorrhagia.tw. (3216)

4 heavy menstru$.tw. (956)

5 heavy period$.tw. (103)

6 dysfunctional uter* bleeding.tw. (838)

7 or/1-6 (6952)

8 progestogen implant*.tw. (19)

9 (contracepti$ adj2 implant$).tw. (1107)

10 (Implanon$ or Jadelle$).tw. (304)

11 Levonorgestrel implant$.tw. (156)

12 etonorgestrel$.tw. (21)

13 8 or 9 or 10 or 11 or 12 (1404)

14 7 and 13 (31)

15 randomized controlled trial.pt. (501215)

16 controlled clinical trial.pt. (93562)

17 randomized.ab. (471788)

18 randomised.ab. (94356)

19 placebo.tw. (211267)

20 clinical trials as topic.sh. (190299)

21 randomly.ab. (328458)

22 trial.ti. (214342)

23 (crossover or cross-over or cross over).tw. (83681)

24 or/15-23 (1337759)

25 exp animals/ not humans.sh. (4675662)

26 24 not 25 (1231078)

27 14 and 26 (4)

Database: **Embase**

Search Strategy:

1 exp Menorrhagia/ (9472)

2 hypermenorrhea.tw. (306)

3 Menorrhagia.tw. (5205)

4 heavy menstru$.tw. (1761)

5 heavy period$.tw. (175)

6 dysfunctional uter$ bleeding.tw. (1070)

7 or/1-6 (11760)

8 exp Medroxyprogesterone Acetate/ (16251)

9 medroxyprogesterone$.tw. (6889)

10 depoprovera$.tw. (309)

11 depo provera$.tw. (1808)

12 8 or 9 or 10 or 11 (17867)

13 7 and 12 (530)

14 Clinical Trial/ (956560)

15 Randomized Controlled Trial/ (589457)

16 exp randomization/ (86255)

17 Single Blind Procedure/ (38135)

18 Double Blind Procedure/ (167151)

19 Crossover Procedure/ (62281)

20 Placebo/ (333233)

21 Randomi?ed controlled trial$.tw. (222624)

22 Rct.tw. (35951)

23 random allocation.tw. (1979)

24 randomly.tw. (431237)

25 randomly allocated.tw. (34337)

26 allocated randomly.tw. (2504)

27 (allocated adj2 random).tw. (810)

28 Single blind$.tw. (24161)

29 Double blind$.tw. (199587)

30 ((treble or triple) adj blind$).tw. (1105)

31 placebo$.tw. (297889)

32 prospective study/ (584539)

33 or/14-32 (2384555)

34 case study/ (67249)

Database: **Ovid MEDLINE(**R) Epub Ahead of Print, In Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily, and Ovid MEDLINE (R) 1946-Present

Search Strategy:

1 exp Menorrhagia/ (4216)

2 hypermenorrhea.tw. (245)

3 Menorrhagia.tw. (3216)

4 heavy menstru$.tw. (956)

5 heavy period$.tw. (103)

6 dysfunctional uter$ bleeding.tw. (838)

7 or/1-6 (6952)

8 exp Medroxyprogesterone Acetate/ (4840)

9 medroxyprogesterone$.tw. (6154)

10 depoprovera$.tw. (25)

11 depo provera$.tw. (781)

12 8 or 9 or 10 or 11 (8049)

13 7 and 12 (102)

14 randomized controlled trial.pt. (501215)

15 controlled clinical trial.pt. (93562)

16 randomized.ab. (471788)

17 randomised.ab. (94356)

18 placebo.tw. (211267)

19 clinical trials as topic.sh. (190299)

20 randomly.ab. (328458)

21 trial.ti. (214342)

22 (crossover or cross-over or cross over).tw. (83681)

23 or/14-22 (1337759)

24 exp animals/ not humans.sh. (4675662)

25 23 not 24 (1231078)

26 13 and 25 (24)

Appendix 2. AMSTAR 2

1. **Did the research questions and inclusion criteria for the review include the components of PICO?**

YES: PICO

Time frame

No

2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?

Partial yes (ALL):

- Review question
- Search strategy
- Inclusion/exclusion criteria
- Risk of bias assessment

Yes (partial + all)

- Meta-analysis/synthesis plan, if appropriate
- A plan for investigating causes of heterogeneity
- Justification for any deviations from the protocol

No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

Yes (ONE)

- Explanation for including only RCTs
- OR explanation for including only non-randomised studies of interventions (NRSI)
- OR explanation for including both RCTs and NRSI

No

4. Did the review authors use a comprehensive literature search strategy?

Partial yes (ALL)

- Searched at least 2 databases (relevant to research question)
- Provided key word and/or search strategy
- Justified publication restrictions (e.g. language)

YES (partial + ALL)

- Searched the reference lists/bibliographies of included studies
- Searched trial/study registries
- Included/consulted content experts in the field
- Where relevant, searched for grey literature
- Conducted search

No

(Continued)

5. Did the review authors perform study selection in duplicate?

Yes (ONE)

- At least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include
- OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder selected by one reviewer

No

---

6. Did the review authors perform data extraction in duplicate?

Yes (ONE)

- At least two reviewers achieved consensus on which data to extract from included studies;
- OR two reviewers extracted data from a sample of eligible studies and achieved good agreement (at least 80 per cent), with the remainder extracted by one reviewer.

No

---

7. Did the review authors provide a list of excluded studies and justify the exclusions?

Partial yes

- Provided a list of all potentially relevant studies that were read in full text form but excluded from the review

Yes (also)

- Justified the exclusion from the review of each potentially relevant study

No

---

8. Did the review authors describe the included studies in adequate detail?

For partial yes (ALL the following)

- Described populations +described interventions
- Described comparators described outcomes
- Described research designs

For yes, should also have ALL the following

- Described population in detail
- Described intervention in detail (including doses where relevant)
- Described comparator in detail (including doses where relevant)
- Described study's setting
- Timeframe for follow-up

No

---

9. Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review? RCT

For partial yes, must have assessed risk of bias from:

- Unconcealed allocation;
- And lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all cause mortality).

For yes, must also have assessed risk of bias from:

- Allocation sequence that was not truly random;

(Continued)

- And selection of the reported result from among multiple measurements or analyses of a specified outcome.

No

---

10. Did the review authors report on the sources of funding for the studies included in the review?

For yes

- Must have reported on the sources of funding for individual studies included in the review. Note: reporting that the reviewers looked for this information but it was not reported by study authors also qualifies

No

---

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? RCT

For yes

- The authors justified combining the data in a meta-analysis
- AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present
- AND investigated the causes of any heterogeneity

No

No meta analysis conducted

---

12. If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?

For yes:

- Included only low risk of bias RCTs;
- OR, if the pooled estimate was based on RCTs and/or NRSI at variable risk of bias, the authors performed analyses to investigate possible impact of risk of bias on summary estimates of effect.

No

No meta analysis conducted

---

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For yes

- Included only low risk of bias RCTs
- OR, if RCTs with moderate or high risk of bias, or NRSI were included the review provided a discussion of the likely impact of risk of bias on the results

No

---

14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?

For yes

- There was no significant heterogeneity in the results
- OR if heterogeneity was present, the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review

No

---

15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?

For yes

(Continued)

- Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias

No

No meta analysis conducted

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For yes

- The authors reported no competing interests OR
- The authors described their funding sources and how they managed potential conflicts of interest

No

Appendix 3. Node-split results. First-line. Menstrual blood loss. (Combined)

COMBINED MEAN BLOOD LOSS (ENDPOINT AND CHANGE FROM BASELINE)

Side		Comparison of Y vs X		Direct		Indirect		Difference		P>|z|
		X	Y	Mean Diff	Std. Err.	Mean Diff	Std. Err.	Mean Diff	Std. Err.	
1	6	Placebo	NSAIDs	−49.9811	25.89066	−11.2014	46.26587	−38.7798	53.00106	0.464
1	7	Placebo	Antifibrinolytics	−68.6471	29.19427	−107.379	44.2173	38.73227	53.00226	0.465
2	3	CVR	COC	27.3509	41.09786	20.18564	72.18571	7.165267	83.14633	0.931
2	9	CVR	Long-cycle Pg	2.100004	53.35153	9.22418	63.76601	−7.12418	83.14139	0.932
3	4	COC	Danazol	−19.1684	57.07587	−65.7967	74.38362	46.62828	93.55745	0.618
3	6	COC	NSAIDs	15.70302	57.24792	15.7019	61.29866	0.001122	83.53626	1
3	10	COC	LNG-IUS	−52.9658	40.29542	−36.1379	71.8173	−16.8278	82.3826	0.838
4	6	Danazol	NSAIDs	48.92792	39.86311	60.84555	65.92257	−11.9176	77.01708	0.877
4	8	Danazol	Luteal Pg	86.4587	57.65394	63.49177	53.01963	22.96694	78.22073	0.769
5	7	Ethamsylate	Antifibrinolytics	−101.31	56.73824	−76.3184	64.7377	−24.9918	85.50179	0.77
6	7	NSAIDs	Antifibrinolytics	−72.6287	57.95434	−30.647	30.11349	−41.9817	65.58373	0.522
6	8	NSAIDs	Luteal Pg	7.499999	54.89114	30.44654	42.10213	−22.9465	69.17822	0.74
7	8	Antifibrinolytics	Luteal Pg	63.47069	42.17429	58.9224	51.59067	4.548289	66.5435	0.946
7	9	Antifibrinolytics	Long-cycle Pg	8.709065	38.78747	−16.4963	75.18427	25.20541	84.59993	0.766
9	10	Long-cycle Pg	LNG-IUS	−21.42	52.94217	−38.2336	63.12108	16.81357	82.38413	0.838

Appendix 4. Node-split results. First-line. Menstrual blood loss (sensitivity analysis)

MEAN BLOOD LOSS AT ENDPOINT

Node-split results - random-effects model

Side		Comparison of Y vs X		Direct		Indirect		Difference		P>|z|
		X	Y	Mean Diff	Std. Err.	Mean Diff	Std. Err.	Mean Diff	Std. Err.	
1	6	Placebo	NSAIDs	−48.6964	18.49676	−28.2365	46.34697	−20.4599	49.89525	0.682
1	7	Placebo	Antifibrinolytics	−95.736	38.58291	−116.152	31.66106	20.41588	49.90111	0.682
2	3	CVR	COC	19.54857	25.13099	93.31438	43.19615	−73.7658	50.53359	0.144
2	9	CVR	Long-cycle Pg	2.100004	29.45055	−71.6779	41.06098	73.77786	50.53056	0.144
3	4	COC	Danazol	−19.5755	39.37223	−93.9778	51.22275	74.40232	64.30718	0.247
3	6	COC	NSAIDs	14.71929	40.18335	−11.4579	43.8228	26.17721	58.97513	0.657
3	10	COC	LNG-IUS	−173.6	18.32955	−33.6154	25.0968	−139.985	31.07766	0
4	6	Danazol	NSAIDs	48.91868	27.65232	53.23686	48.42096	−4.31818	55.73304	0.938
4	8	Danazol	Luteal Pg	73.75836	42.16143	43.6648	37.20711	30.09356	56.12898	0.592
5	7	Ethamsylate	Antifibrinolytics	−101.358	39.86295	−111.91	51.16417	10.5518	64.18923	0.869
6	7	NSAIDs	Antifibrinolytics	−71.3622	42.25772	−58.3115	26.39803	−13.0507	50.32471	0.795
6	8	NSAIDs	Luteal Pg	7.499996	37.07959	6.69817	32.13147	0.801826	49.06452	0.987
7	8	Antifibrinolytics	Luteal Pg	59.54995	30.5242	83.67885	38.17113	−24.1289	48.82551	0.621
7	9	Antifibrinolytics	Long-cycle Pg	8.720853	25.55254	−50.6457	53.22126	59.36651	59.03729	0.315
9	10	Long-cycle Pg	LNG-IUS	−21.42	16.07161	−161.402	26.59992	139.9818	31.07818	0

Appendix 5. Node-split results. First-line. Perception of bleeding improvement

PERCEPTION OF BLEEDING IMPROVEMENT									
Node-split results - random-effects model									
Side	**Side**	**Comparison of Y vs X**		**Direct**		**Indirect**		**Difference**		**P>|z|**
		X	**Y**	**Ln-odds ratio**	**Std. Err.**	**Ln-odds ratio**	**Std. Err.**	**Ln-odds ratio**	**Std. Err.**	
1	6	Placebo	NSAIDs	3.120895	1.077231	0.285072	1.324783	2.835824	1.707476	0.097
1	7	Placebo	Antifibrinolytics	1.150863	1.143165	3.986551	1.268326	−2.83569	1.707476	0.097
4	6	Danazol	NSAIDs	−0.18232	1.431655	−0.94035	1.303436	0.758024	1.936125	0.695
4	8	Danazol	Luteal Pg	−1.59003	0.99435	−0.83198	1.661421	−0.75805	1.93612	0.695
5[a]	6	Ethamsylate	NSAIDs	0.664976	1.263524	0.484471	2.820899	0.180505	3.101458	0.954
5[a]	7	Ethamsylate	Antifibrinolytics	1.034074	1.262739	1.214601	2.821953	−0.18053	3.101458	0.954
6[a]	7	NSAIDs	Antifibrinolytics	1.336838	0.715685	−1.25733	0.987732	2.59417	1.241331	0.037
6	8	NSAIDs	Luteal Pg	−0.37067	1.17565	−1.10953	1.012907	0.738863	1.551687	0.634
7	8	Antifibrinolytics	Luteal Pg	−1.19803	0.630909	−1.43008	1.744104	0.23205	1.859741	0.901
7	9	Antifibrinolytics	Long-cycle Pg	−1.82924	1.147346	1.092652	1.414133	−2.9219	1.821037	0.109
7	10	Antifibrinolytics	LNG-IUS	2.281122	1.111473	−1.10914	1.139989	3.390259	1.556894	0.029
8	10	Luteal Pg	LNG-IUS	2.025794	1.358828	1.593935	1.59729	0.431859	2.073284	0.835
9	10	Long-cycle Pg	LNG-IUS	0.58783	0.895417	3.509751	1.586125	−2.92192	1.821043	0.109

Footnote

[a]The evidence for these comparisons comes from trials that directly compare them.

Appendix 6. Node-split results. First-line. Any adverse event

ANY ADVERSE EFFECT										
Node-split results - fixed-effect model										
Side		**Comparison of Y vs X**		**Direct**		**Indirect**		**Difference**		**P>|z|**
		X	**Y**	**Ln-odds ratio**	**Std. Err.**	**Ln-odds ratio**	**Std. Err.**	**Ln-odds ratio**	**Std. Err.**	
1	2	Placebo	COC	0.772	0.226639	1.326314	1.19228	−0.55431	1.21363	0.648
1	5	Placebo	Antifibrinolytics	0.308553	0.384999	−0.24577	1.150933	0.554326	1.213618	0.648
2	8	COC	LNG-IUS	−0.40547	0.975182	0.14885	0.722438	−0.55432	1.21363	0.648
4	5	NSAIDs	Antifibrinolytics	−0.01835	1.42713	0.172479	0.833552	−0.19083	1.652728	0.908
4	6	NSAIDs	Luteal Pg	0.654926	0.764046	0.4641	1.465517	0.190826	1.652727	0.908
5	6	Antifibrinolytics	Luteal Pg	0.503178	0.335882	0.276984	1.343592	0.226195	1.382645	0.87
5	8	Antifibrinolytics	LNG-IUS	0.167295	0.619065	1.095312	0.842583	−0.92802	1.039433	0.372
6	8	Luteal Pg	LNG-IUS	0.609616	0.647781	−1.27515	0.942485	1.884769	1.150687	0.101

Appendix 7. Node-split results. Second-line. Bleeding improvement (no imputed data)

PBAC IMPROVEMENT (NO IMPUTED VALUES)									
Node-split results - fixed-effect model									
Side		**Comparison of Y vs X**		**Direct**		**Indirect**		**Difference**		**P>|z|**
		X	**Y**	**Coef.**	**Std. Err.**	**Coef.**	**Std. Err.**	**Coef.**	**Std. Err.**	
3	4	NREA	LNG-IUS	−2.35608	0.892178	−0.9155	0.443133	−1.44058	0.996166	0.148
2	3	REA	NREA	0.173453	0.152816	1.614023	0.984374	−1.44057	0.996165	0.148
2	4	REA	LNG-IUS	−0.74204	0.41595	−2.18262	0.90517	1.440576	0.996166	0.148

Appendix 8. Imputation details. Second-line. Pictorial blood assessment chart (PBAC)

INTRODUCTION

The outcome of interest is the probability of bleeding improvement measured by PBAC being under 75 points after treatment. The PBAC < 75 threshold was chosen by review authors as it was the limited used in most trials to define bleeding improvement; some trials also used it as similar to acceptable bleeding improvement (reporting it together as one or the other). We decided to use the same outcome.

However, six studies ((D) Athanatos 2015; (D) Hawe 2003; (D) Meyer 1998; (D) Sesti 2011; (D) Sesti 2012; (D) Vercellini 1999) only reported the mean PBAC score at one year for individuals in each arm (with its standard deviation). In order to include as many relevant studies as possible, we imputed individuals with PBAC improvement for theses studies based on the mathematical relationship between the mean score and the probability of exceeding a given threshold.

METHODS

To transform the data we assumed that n_{ik} individuals are randomised to each arm k of study i, where for individual j =1,…, n_{ik} in arm k of trial i, represents the PBAC score at follow-up. Let represent the PBAC improvement status at follow-up for individual j in arm k of trial i, defined as having a **follow-up PBAC score below pre-defined threshold *h***, i.e.

Equation 1: Figure 70.

Figure 70. Formula 1 second-line treatments imputation.

$$l_{jik} = \begin{cases} 1 & \text{if } y_{jik} \leq h \\ 0 & \text{otherwise} \end{cases}$$

Using equation 1 and assuming all individuals have the same underlying distribution of PBAC scores represented by random variable with representing the mean and the variance of the PBAC score, we can write the probability of PBAC improvement for individuals in arm k of trial i as

Equation 2: Figure 71.

Figure 71. Formula 2 second-line treatments imputation

$$L_{ik} = \Pr(Y_{ik} \leq h) = \Phi\left(\frac{h - \mu_{ik}}{\sigma_{ik}}\right)$$

Therefore, studies providing information on the mean PBAC at 1 year, also provide information on the probability of a PBAC improvement, defined as having a PBAC score lower than the selected threshold *h*. We estimated the number of individuals with PBAC improvement for arm *k* of trial *i* as

Equation 3: Figure 72.

Figure 72. Formula 3 second-line treatments imputation.

$$r_{ik} = \left\lfloor n_{ik} \times \Phi\left(\frac{h - \bar{y}_{ik}}{sd_{ik}} \right) \right\rfloor$$

Where the observed mean and standard deviation of PBAC score at follow-up in arm *k* of trial *i* and represents the 'floor' function, meaning values are rounded down to the nearest integer.

We transformed the mean PBAC measurement at follow-up into the number of people with PBAC improvement, defined as PBAC score under 75 points, using equation where *h* =75 and the other parameters are as reported in the trial.

ASSUMPTIONS AND LIMITATIONS

We assumed that our methods for converting continuous PBAC means would give reliable estimates of the number of patients with PBAC improvement. These methods are based on a mathematical relationship with the assumption of normality of the underlying continuous data (PBAC score). However, it may be that the distribution of PBAC scores is skewed and the normality assumption may not be reasonable. Given the available data, it was not possible to empirically check this assumption.

Appendix 9. Node-split results. Second-line. Bleeding improvement (with imputed data)

Bleeding improvement (PBAC) with imputed data

Node-split results - fixed-effect model

Side		Comparison of Y vs X		Direct		Indirect		Difference		P>|z|
		X	Y	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	
3	4	NREA	LNG-IUS	−2.35608	0.892178	−0.76842	0.41947	−1.58766	0.985868	0.107
1	3	Hysterectomy (*)	NREA	−1.95606	1.110263	−1.22445	1.156875	−0.73161	1.603447	0.648
1	4	Hysterectomy (*)	LNG-IUS	−2.32389	1.088635	−3.0555	1.17725	0.731611	1.603447	0.648
2	3	REA	NREA	0.057813	0.129425	1.121585	0.878548	−1.06377	0.88803	0.231
2	4	REA	LNG-IUS	−0.74204	0.41595	−1.80582	0.784592	1.063776	0.888031	0.231

Appendix 10. Node-split results. Second-line. Amenorrhoea

AMENORRHOEA									
Node-split results - random-effects model									
Side		**Comparison of Y vs X**		**Direct**		**Indirect**		**Difference**		**P>|z|**
		X	**Y**	**Coef.**	**Std. Err.**	**Coef.**	**Std. Err.**	**Coef.**	**Std. Err.**	
2	3	REA	NREA	0.059995	0.22538	−1.05225	1.012026	1.112248	1.037476	0.284
2	4	REA	LNG-IUS	−0.42946	0.629722	0.682783	0.824839	−1.11225	1.037475	0.284
3	4	NREA	LNG-IUS	0.622791	0.792538	−0.48946	0.668774	1.11225	1.037477	0.284

Appendix 11. Node-split results. Second-line. Satisfaction

SATISFACTION									
Node-split results - fixed-effect model									
Side		**Comparison of Y vs X**		**Direct**		**Indirect**		**Difference**		**P>|z|**
		X	**Y**	**Coef.**	**Std. Err.**	**Coef.**	**Std. Err.**	**Coef.**	**Std. Err.**	
6	7	NREA	LNG-IUS	−0.47151	0.212347	−0.45806	0.45638	−0.01345	0.503363	0.979
1	5	Hysterectomy (any/unspecified)	REA	−1.02962	0.781228	0.471634	0.584988	−1.50125	0.975976	0.124
1	7	Hysterectomy (any/unspecified)	LNG-IUS	0.161183	0.535064	−1.34007	0.816231	1.501253	0.975975	0.124
5	6	REA	NREA	0.245228	0.171773	0.258675	0.473147	−0.01345	0.503363	0.979
5	7	REA	LNG-IUS	−0.56241	0.472548	−0.11744	0.262426	−0.44497	0.540527	0.410

Appendix 12. Node-split results. Second-line. Any adverse event

Node-split results - fixed-effect model

Side		Comparison of Y vs X		Direct		Indirect		Difference		P>|z|
		X	Y	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	
5	6	REA	NREA	1.021979	1.162058	−0.3586	0.600226	1.38058	1.307918	0.291
5	7	REA	LNG-IUS	1.060618	0.370122	2.548414	1.092378	−1.4878	1.153378	0.197
3	5	Minimally invasive hysterectomy	REA	−1.051545	1.647347	−0.05968	0.686901	−0.99186	1.784821	0.578
3	6	Minimally invasive hysterectomy	NREA	−0.2258164	0.395163	−1.21768	1.740526	0.991862	1.78482	0.578
6	7	NREA	LNG-IUS	1.589235	0.524404	0.101436	1.02727	1.487799	1.153379	0.197

Appendix 13. Node-split results. Second-line. Any further surgery

Node-split results - fixed-effect model

Side		Comparison of Y vs X		Direct		Indirect		Difference		P>|z|
		X	Y	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	
3	4	REA	NREA	−0.13281	0.186886	−0.5079	0.596236	0.375082	0.624839	0.548
3	5	REA	LNG-IUS	0.430223	0.451275	0.554857	0.465895	−0.12463	0.648619	0.848
1	3	Hysterectomy (*)	REA	3.151015	0.658708	0.1451	2.022371	3.005914	2.126941	0.158
1	4	Hysterectomy (*)	NREA	0	2.014441	3.005928	0.682587	−3.00593	2.126945	0.158
4	5	NREA	LNG-IUS	0.710958	0.427085	0.586324	0.488165	0.124634	0.648619	0.848

Appendix 14. Node-splits results. Second-line. Endometrial ablation, network meta-analysis. Bleeding (pictorial blood assessment chart) improvement

Node-split results - fixed-effect model

Side		Comparison of Y vs X		Direct		Indirect		Difference		P>|z|
		X	Y	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	
1	2	TCRE/rollerball (REA)	Other REA	1.774518	1.116862	−0.2664	0.622647	2.040921	1.278698	0.11
1	3	TCRE/rollerball (REA)	Microwave NREA	0.2204712	0.224719	2.771021	0.709214	−2.55055	0.743965	**0.001**
1	5	TCRE/rollerball (REA)	Bipolar NREA	0.5256407	0.380132	−0.02212	0.424038	0.547757	0.569481	0.336
1	6	TCRE/rollerball (REA)	Balloon NREA	−0.2484614	0.268901	−0.83357	0.527121	0.585112	0.591746	0.323
2	6	Other REA	Balloon NREA	−0.1772065	0.572839	−2.21813	1.143208	2.04092	1.278698	0.11
3	5	Microwave NREA	Bipolar NREA	−2.041626	0.637029	0.508924	0.384288	−2.55055	0.743965	**0.001**
5	6	Bipolar NREA	Balloon NREA	−1.315283	0.477079	−0.12868	0.422944	−1.18661	0.637562	0.063

Appendix 15. Node-split results. Subgroup: endometrial ablation, network meta-analysis. Amenorrhoea

Node-split results - random-effects model

Side		Comparison of Y vs X		Direct		Indirect		Difference		P>|z|
		X	Y	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	
1	2	TCRE/rollerball (REA)	Other REA	0.3445016	0.6185282	−0.0537665	1.142229	0.3982681	1.299354	0.759
1	3	TCRE/rollerball (REA)	Microwave NREA	0.1960558	0.6579212	1.249303	0.817412	−1.053247	1.049358	0.316
1	4	TCRE/rollerball (REA)	Hydrothermal ablation NREA	−0.4245752	0.9597677	−0.3967262	1.100154	−0.027849	1.459963	0.985
1	5	TCRE/rollerball (REA)	Bipolar NREA	0.5899178	0.688005	0.6471101	0.6022771	−0.0571923	0.9142737	0.95
1	6	TCRE/rollerball (REA)	Balloon NREA	−0.1236863	0.6413865	−0.7183315	0.5852692	0.5946452	0.8701993	0.494
2	6	Other REA	Balloon NREA	−0.444686	1.045237	−0.8429552	0.7718783	0.3982692	1.299353	0.759
3	5	Microwave NREA	Bipolar NREA	−2.278869	0.8679116	0.8963039	0.5187321	−3.175172	1.011115	**0.002**
3	6	Microwave NREA	Balloon NREA	−0.1555177	0.8962274	−1.556801	0.6717775	1.401283	1.120048	0.211
4	5	Hydrothermal ablation NREA	Bipolar NREA	1.022239	0.9894131	1.050089	1.073567	−0.0278493	1.45996	0.985
5	6	Bipolar NREA	Balloon NREA	−1.690421	0.5038039	−0.030568	0.6470731	−1.659853	0.820491	**0.043**

Appendix 16. Node-split results. Subgroup: endometrial ablation, network meta-analysis. Satisfaction

Node-split results - fixed-effect model

Side		Comparison of Y vs X		Direct		Indirect		Difference		P>|z|
		X	Y	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	
1	2	TCRE/rollerball (REA)	Other REA	−0.0429798	0.343345	0.687731	1.276226	−0.73071	1.321604	0.58
1	3	TCRE/rollerball (REA)	Microwave NREA	0.0628475	0.2924	−0.05468	0.389666	0.117524	0.487173	0.809
1	4	TCRE/rollerball (REA)	Hydrothermal ablation NREA	0.2876821	0.925235	−1.43955	1.10975	1.727233	1.444855	0.232
1	5	TCRE /rollerball (REA)	Bipolar NREA	0.4961681	0.376293	1.271592	0.395433	−0.77542	0.545861	0.155
1	6	TCRE /rollerball (REA)	Balloon NREA	0.2543976	0.350426	−0.11181	0.304707	0.36621	0.464376	0.43
2	6	Other REA	Balloon NREA	−0.6190392	1.254662	0.111672	0.415286	−0.73071	1.321604	0.58
3	5	Microwave NREA	Bipolar NREA	2.559537	1.498918	0.766708	0.318482	1.792829	1.53238	0.242
3	6	Microwave NREA	Balloon NREA	0.0040057	0.282037	0.067346	0.395626	−0.06334	0.485865	0.896
4	5	Hydrothermal ablation NREA	Bipolar NREA	2.240372	1.074424	0.513138	0.966033	1.727234	1.444855	0.232
5	6	Bipolar NREA	Balloon NREA	−0.9305043	0.332309	−0.62823	0.43405	−0.30228	0.546652	0.58

Appendix 17. Node-split results. Subgroup: endometrial ablation, network meta-analysis. Requirement of further surgery for heavy menstrual bleeding

Node-split results - fixed-effect model

Side		Comparison of Y vs X		Direct		Indirect		Difference		P>|z|
		X	Y	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	
1	2	TCRE /rollerball (REA)	Other REA	−0.2141179	0.267122	−0.24197	0.801564	0.027855	0.844902	0.974
1	6	TCRE /rollerball (REA)	Balloon NREA	−0.5341095	0.351366	−0.50625	0.768375	−0.02786	0.844901	0.974
2	6	Other REA	Balloon NREA	−0.2921364	0.72045	−0.31999	0.441375	0.027855	0.844902	0.974

Appendix 18. Node-split results. Subgroup: endometrial ablation, network meta-analysis. Requirement of further hysterectomy for heavy menstrual bleeding

Node-split results - fixed-effect model

Side		Comparison of Y vs X		Direct		Indirect		Difference		P>|z|
		X	Y	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	
1	2	TCRE/rollerball (REA)	Microwave NREA	−0.1034404	0.3665263	−0.0416137	0.625926	−0.06183	0.725345	0.932
1	4	TCRE/rollerball (REA)	Bipolar NREA	−1.139434	0.9296057	−0.4212295	0.53929	−0.7182	1.074709	0.504
1	5	TCRE/rollerball (REA)	Balloon NREA	−0.07298	0.3106057	−0.3852061	0.570816	0.312226	0.649852	0.631
2	4	Microwave NREA	Bipolar NREA	−1.670996	1.568948	−0.3711225	0.552263	−1.29987	1.663307	0.435
2	5	Microwave NREA	Balloon NREA	0.065958	0.5899163	−0.1301057	0.456586	0.196064	0.74597	0.793
4	5	Bipolar NREA	Balloon NREA	0.1934443	0.4920656	1.238682	0.845778	−1.04524	0.978503	0.285

Appendix 19. GRADE wording

Size of the effect estimate	Suggested statements (replace X with intervention, replace 'reduce/increase' with direction of effect, replace 'outcome' with name of outcome, include 'when compared with Y' when needed)
HIGH certainty of the evidence	
Large effect	X results in a large reduction/increase in outcome
Moderate effect	X reduces/increases outcome X results in a reduction/increase in outcome
Small important effect	X reduces/increases outcome slightly X results in a slight reduction/increase in outcome
Trivial, small unimportant effect or no effect	X results in little to no difference in outcome X does not reduce/increase outcome
MODERATE certainty of the evidence	
Large effect	X likely results in a large reduction/increase in outcome X probably results in a large reduction/increase in outcome
Moderate effect	X likely reduces/increases outcome X probably reduces/increases outcome X likely results in a reduction/increase in outcome X probably results in a reduction/increase in outcome
Small important effect	X probably reduces/increases outcome slightly X likely reduces/increases outcome slightly X probably results in a slight reduction/increase in outcome X likely results in a slight reduction/increase in outcome
Trivial, small unimportant effect or no effect	X likely results in little to no difference in outcome X probably results in little to no difference in outcome X likely does not reduce/increase outcome X probably does not reduce/increase outcome
LOW certainty of the evidence	
Large effect	X may result in a large reduction/increase in outcome The evidence suggests X results in a large reduction/increase in outcome
Moderate effect	X may reduce/increase outcome The evidence suggests X reduces/increases outcome X may result in a reduction/increase in outcome The evidence suggests X results in a reduction/increase in outcome
Small important effect	X may reduce/increase outcome slightly The evidence suggests X reduces/increases outcome slightly X may result in a slight reduction/increase in outcome The evidence suggests X results in a slight reduction/increase in outcome
Trivial, small unimportant effect or no effect	X may result in little to no difference in outcome The evidence suggests that X results in little to no difference in outcome X may not reduce/increase outcome

(Continued)

	The evidence suggests that X does not reduce/increase outcome
VERY LOW certainty of the evidence	
Any effect	The evidence is very uncertain about the effect of X on outcome X may reduce/increase/have little to no effect on outcome but the evidence is very uncertain

WHAT'S NEW

Date	Event	Description
9 February 2023	Amended	Correction of links in Table 2

HISTORY

Protocol first published: Issue 11, 2018
Review first published: Issue 5, 2022

Date	Event	Description
21 June 2022	Amended	Corrections to caption of figure 1 and to Table 5

CONTRIBUTIONS OF AUTHORS

All the authors contributed either to the study design or the original protocol. Two overview authors searched for reviews (JB and MBR), extracted data from the studies on the review (MBR and VJ) and analysed the data (SD and MBR). Three overview authors performed the AMSTAR (two per review, to ensure review's authors were not involved on the quality assessment of their own reviews) (SL, MW, MBR). MBR wrote all the versions of the overview and the graphs. All review authors critically reviewed the manuscript and approved the final version.

DECLARATIONS OF INTEREST

Magdalena Bofill Rodriguez, Julie Brown, Michelle Wise, Cindy Farquhar, Vanessa Jordan and Anne Lethaby have been involved as authors or co-authors of Cochrane Reviews that may be included in this overview of reviews. Magdalena Bofill, Michelle Wise and Vanessa Jordan became involved updating the already selected reviews.

Julie Brown has been employed as a medical writer; we are satisfied that her employer had no financial interest in any intervention of interest to this overview.

Sofia Dias, Sarah Lensen and Jack Wilkinson have no conflict of interest.

Cindy Farquhar, Vanessa Jordan and Anne Lethaby are editors of Cochrane Gynecology and Fertility. They took no part in the editorial process.

SOURCES OF SUPPORT

Internal sources

- None, Other

  None
- The Liggins Institute, The University of Auckland, New Zealand

  Stipend for the first year of MBR's PhD

External sources

- None, Other

None

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we stated that we intended to perform a network meta-analysis of the primary outcomes and two of the secondary outcomes (quality of life and adverse events). In the overview we intended to perform network meta-analysis for all three secondary outcomes to add completeness.

We planned to present subgroup analyses for medical and surgical interventions. As the LNG-IUS was compared to medical and surgical interventions, using different participant characteristics, we decided to subgroup into first- and second-line treatments according to those characteristics.

We added a provision to impute data where missing for primary outcomes and conduct a sensitivity analysis with and without the imputed data.

In the protocol we stated we were going to conduct Bayesian network meta-analysis, but we used Stata, as recommended by one of the statistician authors (SD), because a more user-friendly software programme became available between publishing the protocol and performing the overview.

We changed the original title of the overview to highlight the network meta-analysis, adding 'Overview of Cochrane Reviews and network meta-analysis'.

INDEX TERMS

Medical Subject Headings (MeSH)

Amenorrhea; *Antifibrinolytic Agents [therapeutic use]; *Menorrhagia [drug therapy] [surgery]; Network Meta-Analysis; Progestins [therapeutic use]; Quality of Life; Systematic Reviews as Topic

MeSH check words

Child, Preschool; Female; Humans