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Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding (Review)

Lethaby A, Hussain M, Rishworth JR, Rees MC

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[Intervention Review]

Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Anne Lethaby[1], Munawar Hussain[2], Josephine R Rishworth[3], Margaret C Rees[4]

[1]Department of Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand. [2]St. Michael's Hospital & Bristol Centre for Reproductive Medicine, Bristol, UK. [3]Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand. [4]Nuffield Department of Obstetrics and Gynaecology, University of Oxford, Oxford, UK

Contact address: Anne Lethaby, Department of Obstetrics and Gynaecology, University of Auckland, Private Bag 92019, Auckland, 1142, New Zealand. a.lethaby@auckland.ac.nz.

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ABSTRACT

Background

Heavy menstrual bleeding (HMB) is an important cause of ill health in women and it accounts for 12% of all gynaecology referrals in the UK. Heavy menstrual bleeding is clinically defined as greater than or equal to 80 mL of blood loss per menstrual cycle. However, women may complain of excessive bleeding when their blood loss is less than 80 mL. Hysterectomy is often used to treat women with this complaint but medical therapy may be a successful alternative.

The intrauterine device was originally developed as a contraceptive but the addition of progestogens to these devices resulted in a large reduction in menstrual blood loss. Case studies of two types of progesterone or progestogen-releasing systems, Progestasert and Mirena, reported reductions of up to 90% and improvements in dysmenorrhoea (pain or cramps during menstruation). Insertion, however, may be regarded as invasive by some women, which affects its acceptability as a treatment. Frequent intermenstrual bleeding and spotting is also likely during the first few months after commencing treatment.

Objectives

To determine the effectiveness, acceptability and safety of progesterone or progestogen-releasing intrauterine devices in achieving a reduction in heavy menstrual bleeding.

Search methods

All randomised controlled trials of progesterone or progestogen-releasing intrauterine devices for the treatment of heavy menstrual bleeding were obtained by electronic searches of *The Cochrane Library,* the specialised register of MDSG, MEDLINE (1966 to January 2015), EMBASE (1980 to January 2015), CINAHL (inception to December 2014) and PsycINFO (inception to January 2015). Additional searches were undertaken for grey literature and for unpublished trials in trial registers. Companies producing progestogen-releasing intrauterine devices and experts in the field were contacted for information on published and unpublished trials.

Selection criteria

Randomised controlled trials in women of reproductive age treated with progesterone or progestogen-releasing intrauterine devices versus no treatment, placebo, or other medical or surgical therapy for heavy menstrual bleeding within primary care, family planning or specialist clinic settings were eligible for inclusion. Women with postmenopausal bleeding, intermenstrual or irregular bleeding, or pathological causes of heavy menstrual bleeding were excluded.

Data collection and analysis

Potential trials were independently assessed by at least two review authors. The review authors extracted the data independently and data were pooled where appropriate. Risk ratios (RRs) were estimated from the data for dichotomous outcomes and mean differences (MD) for continuous outcomes. The primary outcomes were reduction in menstrual blood loss and satisfaction; in addition, rate of adverse effects, changes in quality of life, failure of treatment and withdrawal from treatment were also assessed.

Main results

We included 21 RCTs (2082 women). The included trials mostly assessed the levonorgestrel-releasing intrauterine device (LNG IUS) (no conclusions could be reached from one small study assessing Progestasert which was discontinued in 2001) and so conclusions are based only on LNG IUS. Comparisons were made with placebo, oral medical treatment, endometrial destruction techniques and hysterectomy. Ratings for the overall quality of the evidence for each comparison ranged from very low to high. Limitations in the evidence included inadequate reporting of study methods and inconsistency.

Seven studies compared the LNG IUS with oral medical therapy: either norethisterone acetate (NET) administered over most of the menstrual cycle, medroxyprogesterone acetate (MPA) (administered for 10 days), the oral contraceptive pill, mefenamic acid or usual medical treatment where participants could choose the oral treatment that was most suitable. The LNG IUS was more effective at reducing HMB as measured by the alkaline haematin method (MD 66.91 mL, 95% CI 42.61 to 91.20; two studies, 170 women; I^2 = 81%, *low quality evidence*) or by Pictorial Bleeding Assessment Chart (PBAC) scores (MD 55.05, 95% CI 27.83 to 82.28; three studies, 335 women; I^2 = 79%, *low quality evidence*), improving quality of life and a greater number of women continued with their treatment at two years when compared with oral treatment. Although substantial heterogeneity was identified for the bleeding outcomes, the direction of effect consistently favoured the LNG IUS. There was insufficient evidence to reach conclusions on satisfaction. Minor adverse effects (such as pelvic pain, breast tenderness and ovarian cysts) were more common with the LNG IUS.

Ten studies compared the LNG IUS with endometrial destruction techniques: three with transcervical resection, one with rollerball ablation and six with thermal balloon ablation. Evidence was inconsistent and very low quality with respect to reduction in bleeding outcomes and satisfaction was comparable between treatments (low and moderate quality evidence). Improvements in quality of life were experienced with both types of treatment. Minor adverse events were more common with the LNG IUS overall, but it appeared more cost effective compared to thermal ablation within a two-year time frame in one study.

Three studies compared the LNG IUS with hysterectomy. The LNG IUS was not as successful at reducing HMB as hysterectomy (*high quality evidence*). The women in these studies reported improved quality of life, regardless of treatment. In spite of the high rate of surgical treatment in those having LNG IUS within 10 years, the LNG IUS was more cost effective than hysterectomy.

Authors' conclusions

The levonorgestrel-releasing intrauterine device (LNG IUS) is more effective than oral medication as a treatment for heavy menstrual bleeding (HMB). It is associated with a greater reduction in HMB, improved quality of life and appears to be more acceptable long term but is associated with more minor adverse effects than oral therapy.

When compared to endometrial ablation, it is not clear whether the LNG IUS offers any benefits with regard to reduced HMB and satisfaction rates and quality of life measures were similar. Some minor adverse effects were more common with the LNG IUS but it appeared to be more cost effective than endometrial ablation techniques.

The LNG IUS was less effective than hysterectomy in reducing HMB. Both treatments improved quality of life but the LNG IUS appeared more cost effective than hysterectomy for up to 10 years after treatment.

PLAIN LANGUAGE SUMMARY

Use of progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Review question: This Cochrane review has evaluated whether the levonorgestrel-releasing intrauterine system (LNG IUS) reduces heavy menstrual bleeding and whether it is safe and acceptable.

Background: Heavy or excessive menstrual bleeding is a common problem in women before they reach the menopause. Women who feel that their menstrual bleeding is excessive will have reduced quality of life and are likely to seek medical help. A wide variety of treatments, of variable effectiveness, are available for women with heavy bleeding. These include oral tablets, such as non steroidal anti-inflammatory drugs, anti-fibrinolytic drugs, the contraceptive pill and drugs containing progestogen. Surgery, either hysterectomy (removal of the womb) or endometrial ablation (removal of the inner lining of the womb) are also commonly used, often when drug treatments are ineffective. A less invasive alternative to these options is the progestogen-releasing intrauterine system, a device placed inside the womb, which regularly delivers small amounts of progestogen and can also be used for contraception.

Study characteristics: This review contains 21 RCTs conducted up to July 2014 that included 2082 participants with heavy menstrual bleeding. Evidence obtained is current to January 2015.

Key results: Almost all the studies assessed the effects of the LNG IUS and conclusions refer only to this device. The LNG IUS was more effective in reducing heavy menstrual bleeding and improving quality of life than oral medication. Satisfaction with treatment was not assessed in enough trials to know whether this was better with LNG IUS. The evidence suggested that the LNG IUS and techniques used to remove the inner lining of the womb were similarly effective at reducing heavy menstrual bleeding and improving quality of life and satisfaction and the two treatments had similar failure rates. The LNG IUS caused higher rates of some side effects, such as breast tenderness, bloating, weight gain and ovarian cysts, but this did not seem to cause women to stop taking their treatment. The LNG IUS was not as effective as hysterectomy in reducing menstrual blood loss but improvements in quality of life were similar. Although many women trying the LNG IUS eventually went on to have a hysterectomy for their heavy menstrual bleeding, the LNG IUS appeared to have lower overall costs than either endometrial ablation or hysterectomy.

Quality of the evidence: Many of the trials in this review were small (<100 participants) and some were at high risk of bias. Ratings for the overall quality of the evidence for each comparison ranged from very low to high. Limitations in the evidence included inadequate reporting of study methods and inconsistency. One large trial compared the LNG IUS with hysterectomy over a 10-year period and a number of other trials made assessments two years after starting treatment, so we have some information on the long-term effects of treatments. Future research needs to measure satisfaction.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

IUS versus placebo or no treatment for heavy menstrual bleeding

Patient or population: patients with heavy menstrual bleeding
Settings: Any
Intervention: IUS versus placebo or no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo or no treatment	IUS				
Mean PBAC score at 6 months follow-up PBAC chart)		The mean PBAC score at 6 months follow-up in the intervention groups was **99.5 lower** (115.75 to 83.25 lower)		40 (1 study)	⊕⊕◯◯ **low**[1]	

*The basis for the **assumed risk** is the mean risk in the control group . The **corresponding risk** (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).
CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Unclear randomisation method and allocation concealment with minimal follow-up

BACKGROUND

Description of the condition

Heavy menstrual bleeding (HMB) is a common problem in women of reproductive age (Shapley 2004) and has a measurable effect on their quality of life (NICE 2007). It can also lead to iron deficiency anaemia (NICE 2007), which can be life threatening in the most severe cases (Moragianni 2007). The prevalence of HMB typically ranges from 9% to 14% in studies that assessed menstrual loss objectively or from 20% to 52% in studies based on subjective assessment (Fraser 2009; NICE 2007).

HMB, also known as menorrhagia, is clinically defined as menstrual blood loss greater than or equal to 80 mL blood loss per menstrual cycle which can be objectively measured by the alkaline haematin test (Cole 1971; Hallberg 1966) but this measurement of menstrual loss is impractical in routine practice. Another, more indirect, method of measuring menstrual loss is the pictorial blood loss assessment chart (PBAC) which was first reported in 1990 (Higham 1990). This method is highly variable with sensitivity ranging from 58% to 97% and specificity ranging from 52% to 89% (NICE 2007); it is undertaken by the patient herself and has been more commonly used in research in the last decade than the objective alkaline haematin method. However, in practice, the woman's perception of her own menstrual loss is considered the key determinant in her referral and indeed subsequent treatment.

Description of the intervention

The primary objective of treating HMB is to reduce the amount of menstrual blood loss and to improve quality of life. Hysterectomy has traditionally been considered the definitive treatment for HMB and it has been one of the most commonly performed operations in women, with HMB being a leading indication (Farquhar 2002). Although hysterectomy is invariably 100% successful in treating HMB and is associated with high success rates, it is major surgery with a relatively high incidence of short-term complications such as bleeding, infection and wound healing problems, together with a lengthy postoperative recovery period. There have been recent indications that the use of hysterectomy for HMB is declining from previous levels; in an analysis of inpatient hysterectomy rates in the United States between 1998 and 2010, hysterectomy for HMB increased to 274,473 in 2002 and then decreased to 195,231 in 2010 (a decline of 28.9%) (Wright 2013). Given that HMB is a benign condition, many women prefer a less invasive surgical option that conserves the womb (uterus). Endometrial resection and ablation procedures involve the destruction of the endometrium (inner lining of the womb) and the underlying basal glands by various means. These methods are safer than hysterectomy but also can cause complications and there is a high rate of further surgical treatment long term (Fergusson 2013). Thus, alternative medical therapy with the avoidance of possibly unnecessary surgery is an attractive alternative. A wide variety of medications are available to reduce heavy menstrual bleeding but there is considerable variation in practice and uncertainty about the most appropriate therapy (Coulter 1995; Farquhar 1996). Many of these treatments, both hormonal and non hormonal, are first line options, with surgery only being used when medical therapy is ineffective or unsuccessful.

The intrauterine device has primarily been used as a method of contraception. Progesterone or progestogen-releasing intrauterine systems were initially introduced in an effort to reduce intrauterine device expulsion. It became apparent that prolonged use of these systems, when used for contraception, was associated with a profound reduction in menstrual blood loss (Andersson 1994; Berqvist 1983).

Progestasert was the first hormonally impregnated device releasing 65 µg of progesterone per day; it required re-insertion approximately yearly but was discontinued in 2001. The levonorgestrel-releasing intrauterine system (LNG IUS) (Mirena, Bayer Healthcare) has been available to manage heavy menstrual bleeding in the United States since 2009 and even earlier than this in Europe. It is available in more than 100 countries worldwide (Inki 2007) and has been used by more than 9 million women (Mansour 2007). It is a T-shaped device which releases LNG (a potent 19 testosterone-derived progestin) directly into the uterine cavity at a rate of 20 µg/day over a five-year time period and is associated with a profound reduction in menstrual blood loss (Rodriguez 2010). However, insertion is an invasive procedure which may not be acceptable to some women. The device is broader than copper-bearing systems and insertion may require local anaesthesia and dilation of the cervical canal in nulliparous or peri-menopausal women. A disadvantage of the device is frequent and variable intermenstrual bleeding and spotting during the first few months of use (Suvisaari 1996). It is also an expensive intervention should its use be discontinued earlier than the five-year lifespan for which it is licensed as an effective contraceptive. Discontinuation may be because of pelvic discomfort or dissatisfaction with the side effects.

How the intervention might work

Local hormone delivery results in high levonorgestrel levels in the endometrial tissue but systemic circulation levels are low. These effects can appear as early as one month after insertion making it an effective method of non surgical management of HMB (Nilsson 1978). Locally released hormone leads to endometrial thinning, glandular atrophy (decreased size of glands), and inflammation. It leads to a reduction in HMB of more than 80% over three to six months treatment (Reid 2005b) and perceived subjective reduction in HMB is similar to that achieved after endometrial ablative treatments (Kaunitz 2009).

The LNG IUS has been compared favourably to other medical treatments for heavy cyclical blood loss (Milsom 1991). It im-

proves dysmenorrhoea and may reduce the incidence of pelvic inflammatory disease, particularly in those under the age of 25 years, by thickening the utero-cervical mucus. Twenty per cent of the women using the LNG IUS were amenorrhoeic after one year's use whilst still continuing to ovulate (Andersson 1994). It also appears to have reduced the number of women undergoing hysterectomy (Reid 2005b).

Why it is important to do this review

HMB or menorrhagia is a common gynaecological condition and has an enormous effect on quality of life of affected women, and on the healthcare system. In the United States, the direct and indirect cost of management of HMB is approximately USD 1 billion and USD 12 billion, respectively (Liu 2007). Medical management with oral agents includes a variety of hormonal and non hormonal therapies with variable effectiveness and tolerability. This has led women to seek surgical procedures such as endometrial ablation and hysterectomy. Given the risk of complications with all surgery and the high probability of further surgery in women undergoing endometrial destruction, it is important to seek an alternative effective, acceptable and safe treatment for HMB. Since the previous publication of this review in 2005, a number of studies have been conducted to compare the progesterone or progestogen-releasing intrauterine system with other treatment modalities. Therefore, it was important to review these new studies with the aim of improving clinical practice.

OBJECTIVES

To determine the effectiveness, acceptability and safety of the progesterone or progestogen-releasing intrauterine devices in achieving a reduction in menstrual blood flow.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of progesterone or progestogen-releasing intrauterine devices versus no treatment, placebo, or other medical or surgical therapies when used to reduce heavy menstrual bleeding. Quasi-randomised trials were excluded.

Types of participants

Inclusion criteria

- Women of reproductive years with regular heavy periods measured either objectively (by the alkaline haematin method), semi-objectively (by PBAC score) or subjectively (patient perception)

Exclusion criteria

- Postmenopausal bleeding (more than one year from the last menstrual period)
- Irregular menses (periods either less than 21 days or more than 35 days apart) and intermenstrual bleeding (bleeding between periods) 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

Source of recruitment

- Community, primary care, family planning or specialist clinics

Types of interventions

Progesterone or progestogen-releasing intrauterine devices versus no treatment, placebo or any other medical or surgical treatment for the reduction of heavy menstrual bleeding.

Types of outcome measures

Primary outcomes

1) Menstrual bleeding

- Objective assessment of menstrual blood loss (mlL (measured by the alkaline haematin method) (Hallberg 1966) or semi-objective assessment by the pictorial bleeding assessment chart score (PBAC) (Higham 1990)
    - measurement of menstrual blood loss at end of study compared between groups
    - measurement of change from baseline compared between group
    - prevalence of amenorrhoea or hypomenorrhoea after treatment
- Subjective assessment of menstrual blood loss:
    - women's perception of improvement recorded in a reproducible format.

2) Satisfaction with treatment

Secondary outcomes

1) Quality of life: participant's perceived change in quality of life provided this was recorded in a reproducible and validated format (for example SF 12 or SF 36), or subjectively by participant questionnaires.
2) Adverse effects
- proportion of women with adverse effects of any type
- proportion of women with specific individual adverse effects

3) Withdrawal from treatment because of adverse events or any reason
4) Treatment failure
5) Resource cost

Search methods for identification of studies

Searches were performed for all published and unpublished RCTs of progestogen-releasing intrauterine systems for reduction of heavy menstrual bleeding, without language or date restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator (TSC).

Electronic searches

For the latest search (20 January 2015), we searched the following electronic databases, trial registers and websites:
Electronic databases (performed by the MDSG Trials Search Co-ordinator):
- Cochrane Menstrual Disorders and Subfertility Group (MDSG) Specialised Trials Register (see Review Group details for more information)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE
- EMBASE
- CINAHL
- PsycInfo

The search strategies for these electronic databases are displayed in the Appendices of this review (Appendix 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6).
Trial registers and websites (performed by Anne Lethaby):
- MetaRegister of Clinical Trials (MRCT);
- US National Institute of Health (NIH) Clinical Trials Register;
- WHO International Clinical Trials Registry Portal (ICTRP);
- Web of Knowledge register.

Searching other resources

The reference lists of eligible studies and relevant reviews were also searched and the pharmaceutical company that supplies Mirena was contacted to identify further eligible studies for inclusion.

Data collection and analysis

Selection of studies

For the 2015 update of this review, two review authors (AL and MH) conducted an initial screen of titles and abstracts retrieved by the search and obtained the full text of studies that appeared eligible for the review, according to the inclusion criteria. The same two review authors independently examined the full text articles and selected studies that were eligible for inclusion. Disagreements were resolved by discussion. AL corresponded with study investigators, as required, to clarify study eligibility.
For earlier versions of the review, the same selection process was undertaken by at least two review authors (AL and either IC or MR).

Data extraction and management

For the 2015 update of the review, two authors (AL and MH) independently extracted data from the eligible studies. Disagreements were resolved by discussion until agreement was reached.
Data extracted included study characteristics and effect estimates. Where studies had multiple publications, the main trial report was used as the reference and additional details were derived from the secondary papers, as required. AL corresponded with study investigators for additional data on the methods and results, but replies were not always received. Where data were missing, attempts were made to either impute values from similar studies or calculate values from formulas given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of risk of bias in included studies

For the 2015 update of the review, two review authors (AL and JR) independently assessed the included studies for risk of bias, using the Cochrane 'Risk of bias' tool (Higgins 2011). Studies were assessed for allocation (random sequence generation and allocation concealment), blinding (of participants and personnel and separately of assessors), completeness of outcome data, selective reporting and other bias (such as comparability of groups at baseline or other potential source of bias). Each domain was graded as either low risk of bias, unclear or high risk of bias. Source of funding for each study was also noted in the Characteristics of included studies table, although this is not a part of the Cochrane 'Risk of bias' tool. Disagreements were resolved by discussion until consensus was reached.
For previous versions of the review, at least two review authors (AL and IC) independently assessed the included studies for method of randomisation, allocation concealment, blinding, methods of dealing with incomplete data and presence of intention-to-treat analysis and power calculations, and source of funding.
'Risk of bias' assessments are included for each study in the Characteristics of included studies table and for each outcome the

overall risk of bias (for each study) for all studies included in the comparison contribute to the overall quality of evidence for the outcome (see Figure 1; Figure 2). In addition, differences in the risk of bias have been incorporated into the interpretation of review findings by means of sensitivity analyses.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

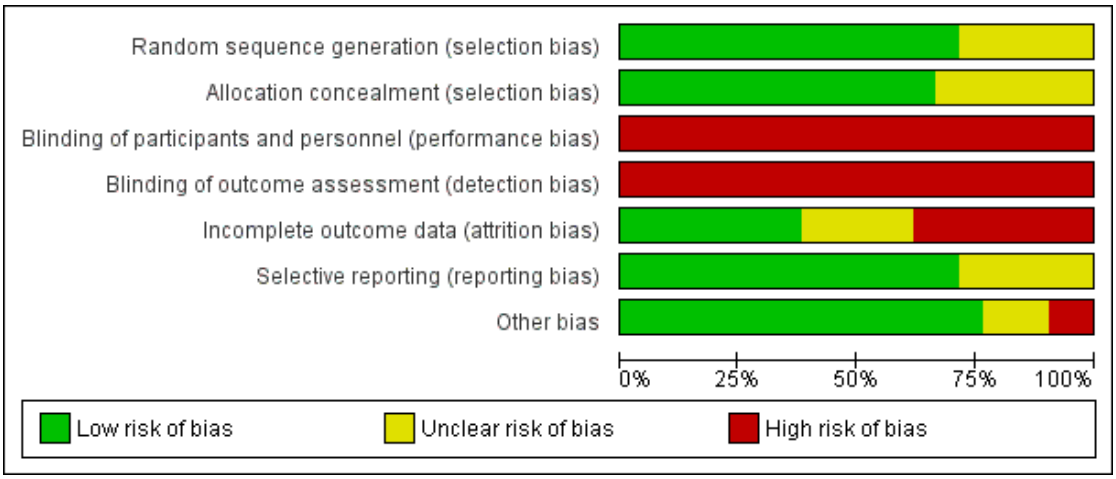
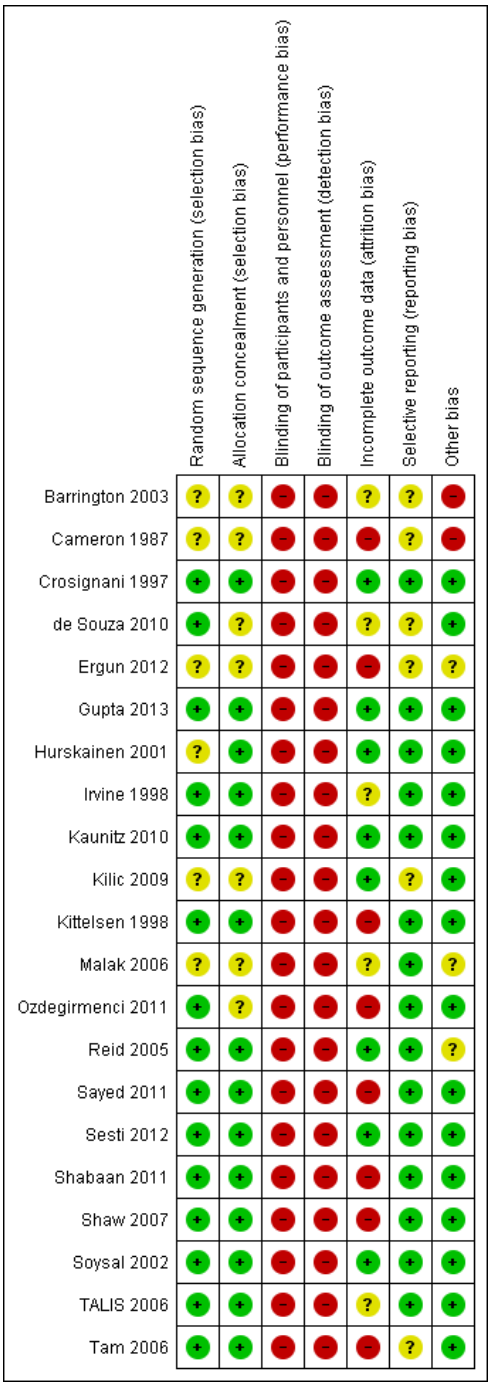


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Measures of treatment effect

For dichotomous data (e.g., treatment failure or amenorrhoea rates), we used the number of events in the two groups to calculate Mantel Haenszel risk ratios (RRs), together with their 95% confidence intervals (CIs). Where there was a statistical difference between the two groups, we calculated numbers needed to treat for benefit (NNTB and numbers needed to treat to harm (NNTH) (estimates of the number of women we would need to receive treatment in order for one woman to receive the benefit or harm). For continuous data (e.g., PBAC bleeding score), we calculated mean differences (MD), with 95% CIs, between treatment groups. Ordinal data (e.g., quality of life scores) were treated as continuous data. Continuous data were only included in the meta-analysis if the underlying distribution of the measurement appeared normal. Data were roughly checked for skewness by calculating the ratio of the mean to its standard deviation; where this value was less than 1, the data were reported in tables as descriptive data. Tables were also used when authors reported their results as a median plus range or when trial results were incomplete (e.g., measures of variance could not be extracted).

In some trials, change scores (from baseline) were reported in preference to, or as well as, final values after treatment. These data were also included in the meta-analysis. Where data were not reported in numbers in the text of the publications, data were estimated from figures or graphs.

Unit of analysis issues

We planned to include only first phase data from cross-over trials, but no cross-over trials were included in the review.

Dealing with missing data

The data were analysed on an intention-to-treat basis, where possible, and attempts were made to obtain missing data from the authors of the included studies, where necessary. Where these were unobtainable and imputation or calculation were not feasible, only the available data were analysed.

Assessment of heterogeneity

We considered whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a meaningful summary. Where studies were pooled in meta-analysis, heterogeneity (variation) between the results of different studies was examined by inspecting the scatter in the data points and their overlap and, more formally, by checking the results of the I^2 value (Higgins 2011). This quantity describes the percentage of total variation across studies that is due to heterogeneity rather than chance. Interpretation of a given degree of heterogeneity will differ according to whether the estimates show the same direction of effect.

A rough guide to interpretation of the I^2 value is as follows (Higgins 2011):

- 0% to 40% might not be important;
- 30% to 60% may represent moderate heterogeneity;
- 50% to 90% may represent substantial heterogeneity;
- 75% to 100% may represent considerable heterogeneity.

Where considerable heterogeneity (I^2 > 90%) was identified from the analyses, the data were not pooled but the individual summary effect estimates were displayed in forest plots without totals.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of trials. As there were fewer than 10 studies contributing to each outcome, the use of a funnel plot to further explore the potential for reporting bias and small-study effects was not possible.

Data synthesis

If the included studies were sufficiently similar, we pooled their results in meta-analysis using both fixed-effect and random-effects models. We presented results in the review using a fixed-effect model where there was no evidence of substantial heterogeneity; otherwise a random-effects model was presented. The following comparisons were made:

- IUS versus placebo;
- IUS versus any other medical treatment;
- IUS versus endometrial ablation;
- IUS versus hysterectomy.

These comparisons were stratified by follow-up interval, where necessary; outcomes were assessed up to 12 months after initiation of treatment or greater than 12 months for outcomes such as satisfaction and treatment failure. Otherwise, data were reported at the end of study.

An increase in the risk of the IUS intervention of a particular outcome which may be beneficial (e.g., satisfaction with treatment) is displayed graphically in the forest plots to the right of the centre line; otherwise, a decrease in the risk (e.g., adverse events) is displayed in the forest plots to the left of the centre line.

Subgroup analysis and investigation of heterogeneity

Where data were available, we conducted subgroup analysis to determine the separate evidence for the following outcomes:

- individual adverse events (e.g., nausea, vaginitis);
- method of assessing menstrual blood loss (alkaline haematin or PBAC scores);
- quality of life domain scores (e.g., physical functioning, general health);
- menstrual bleeding assessments (amenorrhoea, hypomenorrhoea, eumenorrhoea or improvement in bleeding).

When we detected substantial heterogeneity (I^2 > 50%), we explored possible explanations by checking the data, examining clinical and methodological differences between the studies and conducting post hoc sensitivity analyses. We considered any substantial heterogeneity that was identified, especially when there was a variation in the direction of the effect, in our interpretation of the results.

Sensitivity analysis

We conducted sensitivity analyses for the primary outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding eligibility and analysis. These analyses included consideration of whether the review conclusions would have differed if:

- eligibility was restricted to studies without high or unclear overall risk of bias;
- eligibility was restricted to studies of participants with no evidence of fibroids;
- analysis was stratified according to the type of medical treatment, type of endometrial ablation and type of hysterectomy in the control group;
- eligibility was restricted to LNG IUS.

Overall quality of the body of evidence: 'Summary of findings' table

We prepared a 'Summary of findings' table using GRADEPRO. This table evaluated the overall quality of the body of evidence for the main review outcomes (improvement in HMB and satisfaction) and also for failure of treatment, using GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias). Judgements about evidence quality (high, moderate or low) have been justified, documented, and incorporated into reporting of results for each outcome.

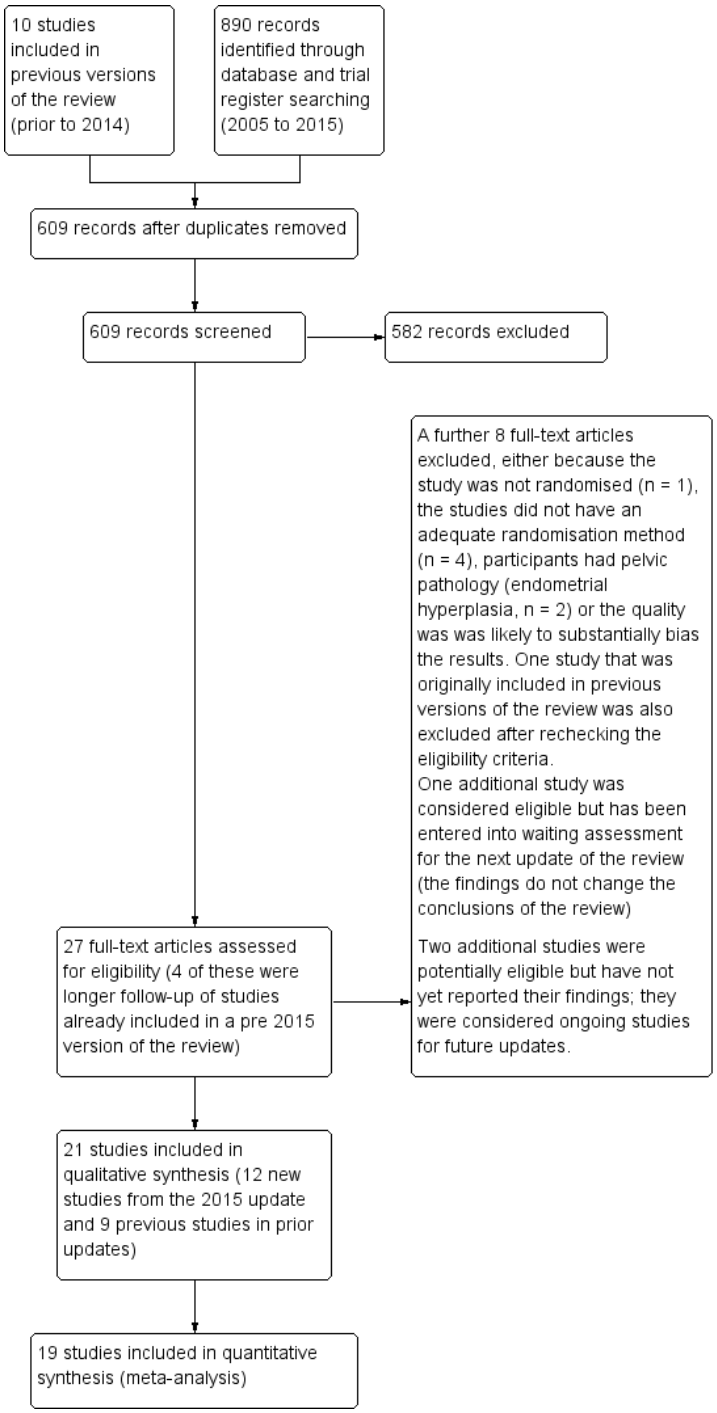
RESULTS

Description of studies

Results of the search

For the 2015 update, a further 25 potentially relevant studies from electronic databases and two studies from searches in additional registers were identified for closer inspection. For detailed search results, see Figure 3.

Figure 3. Study flow diagram.



Included studies

Prior to the 2015 update, 10 randomised controlled trials met the criteria for inclusion in the review. From the 27 potentially relevant studies identified in the 2015 update, 12 met the criteria for inclusion, and four further studies were additional publications (with longer follow-up) for studies already included with the review. Two other studies are ongoing and have not yet reported results (Herman 2013; SHiPP 2013) and three studies are waiting assessment. One study that had been included prior to the 2015 update Lahteenmaki 1998) was excluded because it was no longer considered relevant; the list of outcomes in the review were reduced and this study no longer measured any relevant outcomes. A total of 21 studies (with 2082 participants) were included in the qualitative synthesis of the review. Details of the included studies and those awaiting classification or are ongoing are displayed in Characteristics of included studies, Characteristics of studies awaiting classification; and Characteristics of ongoing studies.

Participants

Participants were mostly recruited either from gynaecology clinics or referred by general practitioners but some women referred themselves by responding to advertisements. In a few trials, women had been scheduled for hysterectomy and in seven trials, women had failed first line medical therapy. A majority of trials excluded women with fibroids of any kind or either those greater than a certain diameter or those large enough to distort the uterine cavity. One research group investigated the effects of treatments separately in women with fibroids (but excluding submucous fibroids of any size distorting the uterine cavity or intramural or subserous fibroids greater than 5 cm in diameter) and women without any evidence of fibroids (in two separate publications). Many studies required women to have completed their families. Menstrual blood loss was usually confirmed by the alkaline haematin method or Pictorial Bleeding Assessment Chart (PBAC) scores prior to the initiation of treatment in consecutive menstrual cycles but in two trials, women were eligible if they considered their menstrual blood flow excessive. In one trial, participants complaining of HMB were only included if they had confirmed adenomyosis, but in two other trials adenomyosis was an exclusion criteria. One trial investigated the effects of treatments for HMB in women taking anticoagulant medication after cardiac valve replacement.

Interventions

The following interventions and comparisons were undertaken.

Comparisons with no treatment

- One trial compared the levonorgestrel-releasing intrauterine system (LNG IUS) with no treatment (in women on anticoagulant medication) (Kilic 2009)

Comparisons with other medical treatments

- One trial compared the LNG IUS with norethisterone (long cycle) (Irvine 1998)
- One trial compared the LNG IUS with medroxyprogesterone acetate (MPA) (10 days) (Kaunitz 2010)
- Two trials compared the LNG IUS with the combined oral contraceptive pill (COC) (Sayed 2011; Shabaan 2011)
- One trial compared the LNG IUS with mefenamic acid (Reid 2005)
- One trial compared the LNG IUS with a control group that was given a variety of medical treatments (tranexamic acid, mefenamic acid, combined oestrogen-progestogen or progesterone alone) (Gupta 2013)
- One trial compared the Progestasert coil with the COC pill, danazol and norethisterone (short course) (Cameron 1987)

Comparisons with surgical treatments

- Three trials compared the LNG IUS with transcervical resection of the endometrium (Crosignani 1997; Kittelsen 1998, Malak 2006)
- Six trials compared the LNG IUS with thermal ablation (Barrington 2003; de Souza 2010; Shaw 2007; Soysal 2002; TALIS 2006; Tam 2006)
- One trial compared the LNG IUS with rollerball ablation (Ergun 2012)
- Three trials compared the LNG IUS with hysterectomy (Hurskainen 2001, Ozdegirmenci 2011; Sesti 2012)

All of the trials except one used the LNG IUS (Mirena) that releases 20 µg/day of levonorgestrel. The device was inserted into the uterine cavity usually within seven days of the last menstrual period. Cameron 1987 used the intrauterine system Progestasert (which was discontinued in 2001), which releases 65 µg of progesterone daily and results from this study were excluded in sensitivity analyses to compare the robustness of the results. This small trial did not evaluate group differences statistically and although randomised, groups were not comparable at baseline. Therefore, most of the results reported in this review pertain to the levonorgestrel-releasing intrauterine system.

Outcomes

The effectiveness of LNG IUS in reducing heavy menstrual bleeding was measured either by PBAC scores or the alkaline haematin method. No trials were identified that measured women's own perception of improvement in HMB. Bleeding outcomes can be summarised as follows.

- Alkaline haematin measurements (ml) at two months (Cameron 1987), three months (Irvine 1998), six months (Kaunitz 2010; Reid 2005), 12 months (Hurskainen 2001; Sayed 2011; Shabaan 2011) or at five and 10 years (Hurskainen 2001).
- PBAC scores were measured at six months (Barrington 2003; Crosignani 1997; Kilic 2009; Reid 2005), 12 months (Crosignani 1997; de Souza 2010; Ergun 2012; Kittelsen 1998; Malak 2006; Sayed 2011; Sesti 2012; Shabaan 2011; Shaw 2007; Soysal 2002; TALIS 2006), 24 months (Kittelsen 1998; Sesti 2012; Shaw 2007; TALIS 2006) and five years (de Souza 2010).
- Categorisation of bleeding patterns as either amenorrhoea, hypomenorrhoea, spotting or normal was based on PBAC scores in 9 trials (Barrington 2003; Crosignani 1997; de Souza 2010; Ergun 2012; Irvine 1998; Malak 2006; Ozdegirmenci 2011; TALIS 2006; Tam 2006).
- One trial measured total menstrual fluid loss (Reid 2005).

Satisfaction with treatment was measured by nine trials (Crosignani 1997; de Souza 2010; Ergun 2012; Hurskainen 2001; Irvine 1998; Malak 2006; Shaw 2007; Soysal 2002; TALIS 2006) mostly at 12 months after the initiation of treatment, but also at longer time points. Satisfaction was typically measured on a five-point scale, from very unsatisfied to very satisfied. Satisfaction rates in this review were scored when participants answered in the top two categories: very satisfied or somewhat/moderately satisfied.

Treatment failure was measured by 10 trials (de Souza 2010; Ergun 2012; Kaunitz 2010; Kittelsen 1998; Malak 2006; Sayed 2011; Shabaan 2011; TALIS 2006; Shaw 2007; Soysal 2002). Treatment failure was defined in various ways. In the trials where LNG IUS was compared with either COC, medroxyprogesterone acetate (MPA) (other medical treatments), treatment failure was defined as either menstrual blood loss >/= 80 mL (alkaline haematin) and >/= 50% reduction from baseline or by the removal or expulsion of the LNG IUS or initiation of different treatment (either medical or surgical). In trials where the LNG IUS was compared with surgery (balloon, rollerball or transcervical resection of the endometrium (TCRE)), treatment failure was defined as an increase of HMB or no improvement in haemoglobin levels, major change in treatment (either expulsion or removal of LNG IUS or initiation of alternative treatment (either medical or surgical)) or PBAC score >/= 75 and re-surgery in the surgical group or removal of LNG IUS.

Withdrawal from treatment for any reason was measured in one trial (Gupta 2013). The reasons given for withdrawal included adverse events, lack of efficacy, lack of tolerability, menopause or personal reasons.

Quality of life was measured by 13 trials (Crosignani 1997; de Souza 2010; Gupta 2013; Hurskainen 2001; Malak 2006; Ozdegirmenci 2011; Sayed 2011; Sesti 2012; Shabaan 2011; Soysal 2002; TALIS 2006; Tam 2006). The scales used included Medical Outcomes Study Short Form 36 Survey questionnaire (SF-36), Psychological General Well-Being Index (PGWBI), Menorrhagia Multi-Attribute Scale (MMAS), EuroQol Group 5-Dimension (EQ-5D) questionnaire and visual analogue scale, RAND-36 item health survey, World Health Organization Quality of Life Short Form (Turkish version) (WHOQOL-BREF-TR), and Health-Related Quality of Life-4 (HRQoL-4). Other quality of life instruments in the included studies that measured specific aspects of quality of life, such as sexual functioning and anxiety were not eligible for the review.

Adverse events were measured in 11 trials (Crosignani 1997; Gupta 2013; Hurskainen 2001; Irvine 1998; Kittelsen 1998; Malak 2006; Ozdegirmenci 2011; Reid 2005; Soysal 2002; TALIS 2006; Tam 2006). These were mostly measured incidentally and were secondary outcomes in the trials. A few trials also measured discontinuation from the study because of adverse events (Irvine 1998; Kittelsen 1998). Some adverse events were not directly compared because they were associated specifically with the mode of treatment, for example, bowel perforation in hysterectomy or expulsion rate of the LNG IUS.

Costs were compared between groups in two trials (Hurskainen 2001; TALIS 2006); one comparing costs of LNG IUS with hysterectomy and the other with thermal balloon ablation.

Duration of follow-up varied between the included studies. The single placebo controlled study had minimal follow-up of three months.Trials comparing the LNG IUS with various types of medical treatment ranged from two months to two years follow-up. This latter trial, ELIPSE, is planning to monitor participants for five and 10 years. Over half of the trials comparing the LNG IUS with endometrial ablation had 12 months follow-up, one had six months follow-up and the remaining three trials had two, three and five years follow-up. Two of the trials comparing hysterectomy with the LNG IUS had 12-month follow-up; in the remaining trial, conducted in Finland, participants were monitored for 10 years. Outcomes from trials with minimal follow-up should be considered with caution. From the case series studies, it is known that menstrual irregularity may be problematic in the first months after insertion of the LNG IUS (Suvisaari 1996); thus, assessment of this method after two or three months may give a misleadingly poor outcome.

Some of the outcomes from the studies could be pooled in the meta-analysis. Other outcomes could not be pooled because the data were heavily skewed or measures of variation were not reported and individual participant data were not available for transformation.

Excluded studies

Prior to the 2015 update, five studies were excluded from those considered potentially eligible; two because there was no indication that they were randomised (Karacaoglu 2001; Romer 2000), one because the LNG IUS arm was not randomised (Milsom 1991), one because only 22% of the participants had HMB (Janssen 1999) and one because it experienced difficulties in recruitment so the trial was terminated (Rogerson 1999). A further study that had been included in previous versions of the review (Lahteenmaki 1998) was excluded in the 2015 update because it no longer measured relevant outcomes.

Of 27 potentially relevant studies retrieved in the 2015 update, a further eight were excluded; one because it was an observational cohort study; four because the randomisation methods were not adequate (participants could choose treatment or allocation was by order of arrival or predefined application order); two because participants had endometrial hyperplasia and one because of a substantial imbalance in the dropout rates between groups. Details of all the excluded studies are presented in Characteristics of excluded studies.

Risk of bias in included studies

Allocation

All included studies were randomised controlled trials, and adequate methods of randomisation (such as computer-generated randomisation, permuted blocks or drawing from a hat) were reported in 15 trials. In the remaining six trials, the method of randomisation was not reported and these studies were considered at unclear risk of bias.

Adequate methods of allocation concealment were undertaken in 14 trials. In the remaining seven trials, measures to conceal allocation were not reported and these studies were scored at unclear risk of bias.

Blinding

All trials were considered at high risk of bias for blinding; mostly it was not feasible to blind participants to the differing nature of the interventions. As a majority of the primary outcomes were self-reported by the participants, this means that assessments also were generally unblinded. These studies were considered at high risk of bias for these domains because knowledge of treatment could have influenced the responses made. One trial (Sesti 2012) attempted to blind participants until randomised allocation was completed. Surgeons and assessors were blinded to allocation but the participants scored the PBAC instrument, quality of life and postoperative pain and the knowledge of treatment may have influenced their responses.

Incomplete outcome data

Eight trials were assessed as at low risk of bias because there were either no, or minimal, dropouts (dropouts were included in the analyses or sensitivity analysis was performed to assess the impact of imputation for missing data). Five trials were considered at unclear risk of bias because dropouts were minimal but differed by randomised group or increased with long-term follow-up. Eight studies were considered at high risk of bias because there was either substantial dropout, a large imbalance in the dropout per group or reasons were not provided for dropouts.

Selective reporting

Fifteen trials were considered at low risk of bias because there was no clear evidence of selective reporting; all prespecified outcomes were clearly reported in the results sections of the papers. Six studies were considered at unclear risk of bias because adverse events were not reported or the outcomes were not clearly specified.

Other potential sources of bias

Sixteen trials were considered at low risk of bias because groups appeared to be comparable at baseline and there was no evidence of any other sources of bias. Three studies were considered at unclear risk of bias because either the authors did not report on participants' characteristics by group, there were unequal numbers in the randomised groups with no explanation given, or it was not clear whether the imbalance in one participant's characteristics at baseline between groups could have resulted in bias. Two trials were considered at high risk of other bias because the primary outcome differed substantially at baseline between groups and analyses were performed without adjustment.

A summary of the quality of the included studies is provided in Figure 1 and Figure 2.

Effects of interventions

See: **Summary of findings for the main comparison** IUS versus placebo or no treatment for heavy menstrual bleeding; **Summary of findings 2** IUS versus any other medical treatment for heavy menstrual bleeding; **Summary of findings 3** IUS versus endometrial ablation for heavy menstrual bleeding; **Summary of findings 4** IUS versus hysterectomy for heavy menstrual bleeding

1 Progestogen-releasing intrauterine system versus placebo or no treatment

One small study (40 women) (Kilic 2009) compared the levonorgestrel-releasing intrauterine device (LNG IUS) with placebo in women taking anticoagulant medication after cardiac valve replacement (where women were at increased risk of heavy menstrual bleeding). At six months follow-up, women had significantly

lower PBAC scores after treatment with LNG IUS compared with placebo (mean difference (MD) -99.50, 95% confidence interval (CI) -115.75 to -83.25) (Analysis 1.1).

2 Progestogen-releasing intrauterine system versus any other medical therapy

Seven trials compared a progestogen-releasing intrauterine device with other medical treatment (Cameron 1987; Gupta 2013; Irvine 1998; Kaunitz 2010; Reid 2005; Sayed 2011; Shabaan 2011). All but one small study (Cameron 1987), used the levonorgestrel-releasing intrauterine device (LNG IUS). LNG IUS was compared with long-cycle norethisterone (Irvine 1998), a 10-day dose of medroxyprogesterone acetate (MPA) (Kaunitz 2010), the oral contraceptive pill in women, without and women with fibroids (Sayed 2011; Shabaan 2011), mefenamic acid (Reid 2005), a variety of medical treatments (chosen by the patient and physician according to preference) (Gupta 2013) (including mefenamic acid, tranexamic acid, norethindrone, a combined oestrogen-progestogen or progesterone only oral contraceptive pill or medroxyprogesterone acetate (MPA) injection). A progesterone impregnated coil (Progestasert) was compared with daily danazol, mefenamic acid during menstruation and norethisterone during days 15 to 25 of the menstrual cycle in a small study of 30 women (Cameron 1987).

Primary outcomes

2.1 Objective and semi-objective measurements of menstrual blood loss

Compared with medical treatment, the progestogen-releasing IUS was associated with significantly reduced menstrual bleeding in most trials measuring this outcome.

Where summary effect measures could be calculated, treatment with the LNG IUS was associated with a significantly greater percentage reduction from baseline by the alkaline haematin method when compared to the oral contraceptive pill (MD 66.91 mL, 95% CI 42.61 to 91.20; two studies, 170 women; I^2 = 81%), or by PBAC scores (MD 55.05, 95% CI 27.83 to 82.28; three studies, 335 women; I^2 = 79%; Analysis 2.2). Two of the trials in this pooled analysis (Sayed 2011; Shabaan 2011) also reported significantly reduced menstrual blood loss at the end of study with LNG IUS compared to the combined oral contraceptive, although substantial heterogeneity meant they couldn't be pooled (Analysis 2.1).

Four other studies where the data could not be pooled confirmed the significant benefits found with the IUS (four studies with alkaline haematin measurement (Cameron 1987; Irvine 1998; Kaunitz 2010; Reid 2005) and one with PBAC score measurement (Reid 2005)); one study found that menstrual fluid loss was significantly reduced with LNG IUS and one other study found a non significant trend towards higher rates of amenorrhoea with LNG IUS. These analyses considered any comparison of the LNG IUS with either medical therapy as a whole, given that women often are given choices of the most appropriate medical treatment, according to their personal circumstances/preference, mefenamic acid or oral progestogens. With regard to data on the delivery method of progestogens (intrauterine device versus oral treatment), two trials compared the LNG IUS with either a long course oral progestogens, norethisterone acetate (NET) or 10-day MPA; in the LNG IUS versus NET comparison, there was no evidence of a significant difference in reduction of HMB but LNG IUS was more successful at reducing HMB than MPA (administered for 10 days). No trials were identified that measured women's own perception of improvement in HMB.

2.2 Satisfaction

There was no evidence that satisfaction rates differed between groups in one small study.

Secondary outcomes

2.3 Quality of life

Quality of life outcomes were measured by three trials. Two trials (170 women) (Sayed 2011; Shabaan 2011) did not find any significant differences between LNG IUS and the oral contraceptive pill in self-rated health (good or excellent) (Analysis 2.8), or in the number of mentally unwell days in the previous month, using the HRQoL-4 scale, but reported significant differences in the number of days participants were physically unwell and number of days lost because of activity limitation between groups (Analysis 2.9). A large good-quality pragmatic trial (Gupta 2013) that compared the LNG IUS with medical treatment (patients randomised to medical treatment received the treatment that was most appropriate to their needs) reported significant improvements in quality of life for a number of domains at two years follow-up (MMAS summary score, SF36 individual scores and EQ5-D), except for mental health (SF36) and EQ5D descriptive scale (Analysis 2.10).

2.4 Adverse events

One large study reported no statistical difference in the rate of serious side effects between groups and there was no statistical difference in the prevalence of most individual side effects. However, the LNG was associated with a significantly higher prevalence of pelvic pain (RR 2.68, 95% CI 1.00 to 7.18; I^2 = 0%; three studies, 784 women), breast tenderness (RR 2.85, 95% CI 1.29 to 6.29; I^2 = 0%; three studies, 244 women) and ovarian cysts (RR 3.28, 95% CI 1.31 to 8.21; I^2 = 0%; three studies, 784 women) (Analysis 2.12). There was no evidence of a statistical difference

between groups in the withdrawal from treatment because of side effects.

2.5 Withdrawal from treatment

One large study reported on the proportions of women who were still on treatment at two-year follow-up (Gupta 2013). The reasons for discontinuation included adverse effects, lack of efficacy, personal reasons, lack of tolerability and menopause. Women with the LNG IUS were significantly less likely to withdraw from treatment within the two years than those allocated to medical treatment (RR 0.58, 95% CI 0.49 to 0.70; NNTB = 4, one study, 571 women) (Analysis 2.14).

2.6 Failure of treatment

Failure of treatment was significantly less likely with LNG IUS compared to medical treatment (RR 0.27, 95% CI 0.18 to 0.40; I^2 = 62%; NNTH = 3, three studies, 327 women) (Analysis 2.15).

Exploration of heterogeneity and sensitivity analyses

Substantial heterogeneity was identified when studies were pooled for assessment of reduction in HMB. Two trials at high overall risk of bias measured menstrual blood loss at the end of the study in two different groups of participants: those with no fibroids and those with fibroid-related HMB by two different methods, alkalin haematin and PBAC scores. Although the summary estimates varied for HMB outcomes, the direction of effect always favoured the LNG IUS. The comparator was mostly the oral contraceptive pill but one study also compared the LNG IUS with MPA, an oral progestogen. The benefits found with LNG IUS in the forest plots were confirmed by studies at low risk of bias, which were not able to be pooled. There were generally too few studies to perform many sensitivity analyses. Adverse events were mainly recorded by studies at low risk of bias. For one outcome, withdrawal from treatment because of adverse events, the removal of a study at unclear overall risk of bias did not affect the findings. Thus, sensitivity analyses suggested that the findings were not influenced by trial quality, or women's fibroid status. We planned a sensitivity analysis restricting inclusion to LNG IUS studies only, but since only studies of LNG IUS were considered in this update, the planned sensitivity analyses were not performed.

3 Progestogen-releasing intrauterine system versus endometrial ablation

Three trials compared the LNG IUS with transcervical resection of the endometrium (TCRE) (Crosignani 1997; Kittelsen 1998; Malak 2006),;one trial compared LNG IUS with rollerball ablation (Ergun 2012) and.six trials compared LNG IUS with thermal balloon ablation (Barrington 2003; de Souza 2010; Shaw 2007; Soysal 2002; TALIS 2006; Tam 2006).

Primary outcomes

3.1 Objective and semi-objective measurements of HMB

Findings were mixed with regard to bleeding outcomes. PBAC scores were significantly lower after treatment with ablation in two studies (Crosignani 1997; Soysal 2002), they were significantly lower in two other studies (both using balloon as control) in the LNG IUS groups (Shaw 2007; TALIS 2006), and there was no evidence of a significant difference between groups in the remaining trials measuring this outcome (Barrington 2003; Ergun 2012; Kittelsen 1998; Malak 2006). When menstrual bleeding was categorised in terms of its flow (amenorrhoea, hypomenorrhoea etc), there was no evidence of a difference in amenorrhoea or hypomenorrhoea rates after treatment between groups, but eumenorrhoea rates were significantly higher in women undergoing ablation (RR 0.55, 95% CI 0.30 to 1.00; I^2 = 61%; three studies, 160 women) and improvement in bleeding pattern was significantly more likely in women with the LNG IUS (RR 1.20, 95% CI 1.02 to 1.41; I^2=40%; three studies, 172 women) (Analysis 3.2). No trials were identified that measured women's own perception of improvement in HMB.

3.2 Satisfaction

There was no evidence of a difference in satisfaction rates between groups.

Secondary outcomes

3.3 Quality of life

Quality of life was measured by five trials, only two of which could be displayed in forest plots (TALIS 2006; Tam 2006). There was no evidence of a significant difference in most of the quality of life domains, with the exception of significantly improved general health (MD -14.40, 95% CI -22.63 to -6.17; one trial 33 women), social functioning (MD -6.70, 95% CI 12.82 to -0.58; one trial, 33 women), emotional role limitation (MD -10.10, 95% CI -17.03 to -3.17, one trial, 33 women) and mental health (MD -11.20, 95% CI -17.08 to -5.32, one trial, 33 women) in participants having endometrial ablation when compared to LNG IUS in one trial measuring the SF36. In three other trials also measuring SF36, no significant differences in domains between groups was identified, except for role limitations due to physical functioning; this was significantly improved in the ablation when compared to the LNG IUS group in one trial. Another trial assessed outcomes at five years (de Souza 2010). It found that physical and emotional wellbeing, assessed by participants as responses to a questionnaire, were significantly improved in those having LNG IUS compared

to endometrial ablation but no differences were found in psychological wellbeing, as assessed by the Psychological General Wellbeing Index.

3.4 Adverse events

Women undergoing ablation were significantly less likely to have side effects overall when compared to LNG IUS (RR 2.1, 95% CI 1.4 to 2.9; I^2 = 0; NNTB = 4, three studies) and some side effects were significantly more common in the LNG IUS group: breast pain (RR 7.57, 95% CI 1.78 to 32.23; I^2 = 0%; three studies, 201 women), weight gain (RR 2.60, 95% CI 1.16 to 5.84; I^2 = 0%; two studies, 141 women), bloating (RR 4.57, 95% CI 1.63 to 12.82; I^2 = 0%; two studies, 141 women) and acne or greasy skin (RR 8.40, 95% CI 1.57 to 44.76; I^2 = 0%; three studies, 201 women) (Analysis 3.10).

3.5 Failure of treatment

Results were also mixed for treatment failure which was measured up to 12 months and greater than 12 months follow-up. Within the first year after surgery, treatment failure appeared to be more likely in the LNG IUS group than in the endometrial ablation group (at threshold of significance level of P = 0.05) (RR 1.58, 95% CI 0.99 to 2.52; I^2 = 0%; six studies, 390 women), but there was no evidence of a significant difference between groups at longer follow-up.(Analysis 3.11)

3.6 Resource cost

One trial published in 2006 found that the expected cost of treatment with LNG IUS was NZD 1241 compared to NZD 2418 for balloon ablation. This finding was robust to sensitivity analysis which included a 25% decrease in the price of primary cost drivers and to variations in the rates of failed treatment.

Exploration of heterogeneity and sensitivity analyses

There were insufficient studies contributing to each outcome to undertake many sensitivity analyses. Where these could be performed, some differences were noted. In the forest plot measuring PBAC score at 12 months, substantial heterogeneity was demonstrated in the two studies measuring this outcome, one at low risk and the other at unclear risk of bias. When the study at unclear risk of bias was excluded, the PBAC score was significantly improved in women undergoing ablation when compared with LNG IUS. This finding was supported by the findings from the other study at low risk of bias which could not be pooled. The reported findings were not influenced by the type of endometrial ablation that was undertaken, or by whether the women had fibroids. Substantial heterogeneity was also identified in satisfaction rates in the subgroup, from one to five years follow-up. Both studies were at high overall risk of bias and the comparator was thermal balloon ablation. However, one of these studies measured satisfaction five years after treatment was initiated, while the other used different questioning after two years follow-up. Differences in the timing of the outcome and the questions asked may explain the discrepant findings between the two trials. As the included studies only assessed the LNG IUS, it was not possible to undertake the planned sensitivity analysis restricting to only studies of LNG IUS.

4 Progestogen-releasing intrauterine system versus hysterectomy

Three trials compared LNG IUS with hysterectomy, one where abdominal, vaginal or laparoscopic hysterectomy were performed, another where only laparoscopic supracervical hysterectomy was performed and for the other, the type of hysterectomy was not described (Hurskainen 2001; Ozdegirmenci 2011; Sesti 2012). These three studies were of unclear risk of bias, high risk of bias and low risk of bias, respectively.

Primary outcomes

4.1 Objective and semi-objective measurements of HMB

One trial at moderate overall risk of bias reported that the PBAC score was significantly lower after hysterectomy than in women with LNG IUS at 24 months (median 3.7 versus 56.4) but not at 12 months follow-up (median 3.7 versus 3.5) (Sesti 2012). No trials were identified that measured women's own perception of improvement in HMB.

4.2 Satisfaction

There was no evidence of a significant difference in satisfaction with treatment in one trial.

Secondary outcomes

4.3 Quality of life

One study at high risk of bias reported no significant differences in quality of life scales (physical, psychological, social and environmental domains) between groups (Ozdegirmenci 2011) and another study of unclear risk of bias also did not find evidence of a significant difference in SF36 domains, EQ-5D score or a visual analogue score (VAS) general health score at 10 years follow-up (Hurskainen 2001). One study (72 women) at moderate risk of bias found improved emotional role and mental health scores (SF36) in women with LNG IUS compared with hysterectomy (MD 16.10, 95% CI 8.88 to 23.32 and MD 36.80, 95% CI 30.37 to 43.23, respectively) and significantly lower pain scores (SF36) in those having hysterectomy compared to LNG IUS (MD -14.80,

95% CI -23.31 to -6.29) (Sesti 2012) (Analysis 4.4). In this trial, the other SF36 scores did not differ significantly between groups.

4.4 Adverse events

With regard to adverse events, wound infection and an increase in back pain was significantly more common in women having hysterectomy (RR 0.17, 95% CI 0.05 to 0.66; two studies, 307 women (Analysis 4.6) and RR 0.58, 95% CI 0.42 to 0.80, one study, 232 women (Analysis 4.7), respectively) than those with LNG IUS. The prevalence of ovarian cysts was significantly greater in women with the LNG IUS than those having hysterectomy (RR 2.72, 95% CI 1.24 to 5.97, one study 180 women) (Analysis 4.7).

4.5 Resource cost

Total health care costs and product losses per women were significantly lower in women with LNG IUS than those having hysterectomy at 12 months follow-up (USD 1530, 95% CI 1203 to 1858 versus USD 4222, 95% CI 3808 to 4636) in one study published in 2001. Women in this trial were monitored for a further nine years and at 10-year follow-up, 46% who were initially treated with LNG IUS had had a hysterectomy. Costs were still substantially lower in the LNG IUS group (discounted rate USD 3423) than in the hysterectomy group (USD 4937).

Exploration of heterogeneity and sensitivity analyses

No heterogeneity was identified. Sensitivity analyses suggested that the findings were not influenced by trial quality, women's fibroid status or type of hysterectomy. We planned a sensitivity analysis restricting inclusion to LNG IUS studies only, but since only studies of LNG IUS were considered in this update, the planned sensitivity analyses were not performed.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

IUS versus any other medical treatment for heavy menstrual bleeding

Patient or population: patients with heavy menstrual bleeding
Settings: Any
Intervention: IUS versus any other medical treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Any other medical treatment	IUS				
Percentage reduction in blood loss at end of study (from baseline) - Alkaline haematin method		The mean percentage reduction in blood loss at end of study (from baseline) - alkaline haematin method in the intervention groups was **66.91 higher** (42.61 to 91.2 higher)		170 (2 studies)	⊕⊕◯◯ **low**[1,2]	
Percentage reduction in blood loss at end of study (from baseline) - PBAC score		The mean percentage reduction in blood loss at end of study (from baseline) - PBAC score in the intervention groups was **55.05 higher** (27.83 to 82.28 higher)		335 (3 studies)	⊕⊕◯◯ **low**[1,3]	
Proportion of women satisfied with treatment	**444 per 1000**	**635 per 1000** (346 to 1000)	**RR 1.43** (0.78 to 2.62)	40 (1 study)	⊕⊕⊕◯ **moderate**[4]	
Failure of treatment	**379 per 1000**	**102 per 1000** (68 to 152)	**RR 0.27** (0.18 to 0.4)	327 (3 studies)	⊕◯◯◯ **very low**[1,2,5]	

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (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).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Substantial attrition
[2] One trial had a different population group
[3] Substantial heterogeneity
[4] Attrition greater in the NETgroup
[5] This outcome measured in different ways by the trials

IUS versus endometrial ablation for heavy menstrual bleeding

Patient or population: patients with heavy menstrual bleeding
Settings: Any
Intervention: IUS versus endometrial ablation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	IUS versus endometrial ablation				
PBAC score at 12 months	See comment	See comment	Not estimable	122 (2 studies)	⊕○○○ **very low**[1,2]	Substantial heterogeneity so trials not combined. The high risk of bias trial reported no difference between treatments and the trial with a lower risk of bias reported that PBAC score was significantly lower with endometrial ablation
Proportion of women satisfied with treatment - After 1 year and up to 5 years follow-up	**824 per 1000**	**922 per 1000** (782 to 1000)	**RR 1.12** (0.95 to 1.31)	102 (2 studies)	⊕⊕○○ **low**[3,4]	
Treatment failure - Up to 12 months follow-up	**124 per 1000**	**195 per 1000** (122 to 312)	**RR 1.58** (0.99 to 2.52)	390 (6 studies)	⊕○○○ **very low**[5,6]	
Proportion of women satisfied with treatment - Within one year follow-up	**811 per 1000**	**770 per 1000** (689 to 868)	**RR 0.95** (0.85 to 1.07)	317 (5 studies)	⊕⊕⊕○ **moderate**[7]	

Treatment failure - More than 12 months follow-up	**230 per 1000**	**255 per 1000** (166 to 394)	**RR 1.11** (0.72 to 1.71)	259 (4 studies)	⊕○○○ **very low**[5,6]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] One of the two studies was at high risk of bias
[2] Substantial heterogeneity - the poor quality study showed no difference and the moderate quality study showed a significant difference
[3] Unclear allocation concealment in one trial and attrition in both trials
[4] Substantial heterogeneity
[5] Substantial attrition
[6] Outcome measured in different ways
[7] Substantial attrition in 2 trials

IUS versus hysterectomy for heavy menstrual bleeding

Patient or population: patients with heavy menstrual bleeding
Settings: Any
Intervention: IUS versus hysterectomy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	IUS versus hysterectomy				
Satisfaction with treatment (5 year follow-up)	930 per 1000	940 per 1000 (875 to 1000)	RR 1.01 (0.94 to 1.08)	232 (1 study)	⊕⊕⊕⊕ high	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
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Very low quality: We are very uncertain about the estimate.

DISCUSSION

Summary of main results

This review has assessed the effectiveness and safety of the levonorgestrel-releasing intrauterine device (LNG IUS) in 20 studies with 2052 participants (an additional small trial of the first hormonally impregnated device, Progestasert (now discontinued) was at high risk of bias and did not present between-group differences). The LNG IUS was compared with placebo in one trial, with medical treatments in seven trials, with endometrial ablation in 10 trials and with hysterectomy in three trials.

The LNG IUS was compared with placebo in women having cardiac valve replacement and their heavy menstrual bleeding was considered a potential side effect of their use of anticoagulant medications. Although the LNG IUS was associated with a reduced menstrual blood loss after six months of approximately 100 Pictorial Bleeding Assessment Chart (PBAC) points, the mean score (155.6) after treatment was still considered within the range of heavy menstruation. Quality of life and satisfaction were not measured, so it is not possible to determine whether women found the treatment beneficial.

There was low level but consistent evidence that the LNG IUS improved bleeding outcomes and was less likely to fail when compared with a range of medical treatments for heavy menstrual bleeding (HMB), although there was insufficient evidence to determine whether this influenced satisfaction. Two studies by the same authors confirmed that the benefits in reduction of HMB with the LNG IUS were found in both fibroid-related and idiopathic HMB when compared with the oral contraceptive pill but both of these studies were at high overall risk of bias. It is important to note that participants with fibroid-related menorrhagia were excluded if they had submucous fibroids of any size distorting the uterine cavity or intramural or subserous fibroids greater than 5 cm in diameter. The improvement in quality of life was significantly greater with LNG IUS compared to either usual medical treatment or the oral contraceptive pill, except for measures of mental health. Women were also more likely to be continuing with their LNG IUS treatment at two-year follow-up than those undergoing usual medical treatment. Some side effects (pelvic pain, breast tenderness and ovarian cysts) were more common with the LNG IUS.

When the LNG IUS was compared with endometrial ablative methods, evidence was mixed and inconsistent and mostly of low or very low overall quality. There was no evidence of a significant difference in bleeding outcomes, satisfaction, quality of life or rate of failure between treatments. The LNG IUS was more likely to cause breast pain, weight gain, bloating and acne or greasy skin, all adverse progestogenic effects. One trial conducted in New Zealand suggested that the LNG IUS was more cost effective than thermal balloon ablation.

The evidence from trials comparing the LNG IUS with hysterectomy was either high or moderate overall quality for the primary outcomes. Women having a hysterectomy had significantly reduced heavy menstrual bleeding in comparison to those using the LNG IUS, but hysterectomy was less cost effective when compared to those having the LNG IUS, in spite of the high rate of hysterectomy in the LNG IUS group at long-term follow-up (46% in 10 years in one trial); quality of life and satisfaction were increased regardless of randomised treatment. One of the three studies included women with adenomyosis; in this study, quality of life was improved with both hysterectomy and the LNG IUS. Adverse event profiles differed: hysterectomy was associated with more wound infection and back pain and the LNG IUS increased the incidence of ovarian cysts.

Overall completeness and applicability of evidence

The review included 21 studies that compared the progestogen-releasing intrauterine system with placebo, medical treatment, endometrial ablation or hysterectomy in women with heavy menstrual bleeding. Some of the women in the trials had fibroid-related bleeding (excluding large intramural/subserous fibroids and submucous fibroids causing distortion) and in others the heavy bleeding was associated with conditions such as adenomyosis or anticoagulant therapy. The effectiveness of the LNG IUS on bleeding outcomes was assessed in various ways: objectively by the alkaline haematin method, semi-objectively by scores on the PBAC or according to definitions of menorrhagia or hypomenorrhoea. The findings with respect to HMB seemed consistent regardless of the method of measurement.

Reduction of HMB should correlate with improving quality of life. In the United Kingdom, NICE has provided a working definition of HMB based on quality of life, rather than measured blood loss (NICE 2007). It defines HMB as "excessive menstrual blood loss which interferes with a woman's physical, emotional, social and material quality of life, and which can occur alone or in combination with other symptoms" and emphasises that treatment should aim at improving quality of life measurements. Treatment with the LNG IUS generally improved health-related quality of life measurements, irrespective of the quality of life instrument used and this treatment improved quality of life when compared to medical treatment, and was at least as satisfactory as surgery, either endometrial ablation or hysterectomy. Few studies measured satisfaction and generally this did not differ between treatments.

LNG IUS was associated with a number of progestagen-related adverse events in the included studies but there was no evidence that these effects resulted in increased withdrawal from treatment. Incidence of ovarian cysts was increased but these were generally symptomless and had a high rate of resolution (Hurskainen 2001).

Only two studies measured comparative costs; one compared the LNG IUS with thermal balloon ablation (TALIS 2006) and the

other compared the LNG IUS with hysterectomy for up to 10 years follow-up (Hurskainen 2001). The LNG IUS was generally more cost effective when compared to surgery. In the latter trial, at 10 years follow-up, 46% of the women allocated to the LNG IUS eventually underwent hysterectomy but the discounted direct and indirect costs remained substantially lower than in the hysterectomy group.

Many of the trials in this review were small (<100 participants) and some were at high risk of bias which means findings are sometimes inconsistent. One large trial compared the LNG IUS with hysterectomy over a 10-year period and a number of other trials made assessments two years after starting treatment, so we have some information on the long-term effects of treatments. Future research needs to measure satisfaction.

Quality of the evidence

Ratings for the overall quality of the evidence for each comparison ranged from very low to high(Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4). Limitations in the evidence included inadequate reporting of study methods and heterogeneity.

Overall, the risk of bias in the included trials varied. All of the trials were had unblinded participants, mostly because of the nature of the interventions. Although the primary bleeding outcome was sometimes measured objectively, in some trials, women were still required to estimate their bleeding by filling in a pictorial chart and it was not possible to exclude the likelihood that knowledge of their treatment influenced their responses. Over half of the included studies reported adequate allocation procedures and allocation concealment but less than half either had minimal missing data or used measures to prevent bias from attrition and lost to follow-up. Further details on the quality of the evidence is reported in Figure 1; Figure 2.

Many of the trials in this review were small (<100 participants). One large trial compared the LNG IUS with hysterectomy over a 10-year period and a number of other trials made assessments two years after starting treatment, so we have some information on the long-term effects of treatments. Future research needs to measure satisfaction.

Potential biases in the review process

Efforts were made to retrieve all eligible studies by implementing a comprehensive search strategy which included searches for grey literature, but it is not possible to exclude the likelihood that some unpublished studies were missed. Attempts to make contact with the company that produces Mirena, the levonorgestrel-releasing intrauterine system, were not successful. Procedures to reduce other potential bias in the review process, such as duplicate selection of studies, data extraction and quality assessment were followed.

Agreements and disagreements with other studies or reviews

Most studies comparing medical treatments for HMB have concluded that the LNG IUS is the most effective option, with the additional advantage that it offers contraception (NICE 2007) and the progestogen component of menopausal hormone therapy (Baldwin 2013; Somboonporn 2011). Reviews have generally concluded that the LNG IUS offers a considerable advantage to other medical treatments in reducing HMB (Kaunitz 2012; Matteson 2013; NICE 2007), with median percentage reductions often exceeding 90%, certainly in the short term, but these reviews have not been able to determine whether the benefits persist long term and whether these translate into reduced adverse events. The long-term results of the ECLIPSE trial (Gupta 2013), included in this review, may be able to provide answers. This large trial found that the LNG IUS improved quality of life when compared to usual medical treatment for up to two years and a large observational study (Xu 2014), undertaken in several countries in the Asia Pacific region, also found that both satisfaction with treatment and quality of life measures were greater in women using the LNG IUS when compared to oral medical treatments (antifibrinolytics, oral progestins or the contraceptive pill), although both groups achieved benefits over time. Another review (You 2006) reported that LNG IUS was 20% less costly than oral medical treatment (mainly because of the high proportion of women in this latter group requiring additional surgical treatment) and also more effective.

With respect to minimal surgery, two systematic reviews have suggested that the LNG IUS appears to be at least as effective as endometrial ablation (Middleton 2010; Kaunitz 2009) (although Middleton acknowledges that evidence is limited), with similar failure rates and quality of life.

Agreement is more mixed with regards to comparisons with hysterectomy which generally focus on quality of life and costs; these studies are strongly influenced by the perspective of the health system in the country of origin. One cost effectiveness review with a UK perspective (Roberts 2011) concluded that hysterectomy was the preferred strategy for the first treatment of HMB when three options were compared: hysterectomy, endometrial ablation and LNG IUS. Although hysterectomy was more expensive, it produced more quality-adjusted life years (QALYs), with the incremental cost effectiveness ratio for hysterectomy when compared with LNG IUS being GBP 1440 per additional QALY. The results were highly sensitive to the utility values used in the analysis. Another review (You 2006), using a healthcare Hong Kong perspective, concluded that hysterectomy was the most effective option (comparison of hysterectomy, endometrial ablation, LNG IUS and medical therapy) with the highest cost. The in-

cremental cost per additional QALY gained by hysterectomy was USD 23,500. The hysterectomy group gained a higher number of QALYs than LNG IUS, oral medical treatment and endometrial ablation groups 99%, 99% and 98% of the time and was more costly than the other three groups over 85% of the time. Another UK cost utility study (Clegg 2007) compared the five-yearly cost of LNG IUS followed by hysterectomy, LNG IUS followed by endometrial ablation, immediate endometrial ablation by either thermal balloon or microwave and hysterectomy. LNG IUS followed by endometrial ablation dominated all the alternative treatments. By contrast, a review (Ganz 2013), using a US payer perspective, concluded that the LNG IUS resulted in the lowest treatment costs and the fewest number of hysterectomies performed over five years compared with all other initial strategies and resulted in the most QALYs gained among non surgical options. Initial treatment with LNG IUS was the least costly and most effective option for women desiring to preserve their fertility. The discrepancy between the findings of these reviews is likely to relate to differences in the methods used and the cost input. However, assuming a USD 50,000 per QALY, LNG IUS treatment was either the dominant or a cost effective strategy and its overall associated costs were lower than those of other treatments for heavy menstrual bleeding.

AUTHORS' CONCLUSIONS

Implications for practice

The levonorgestrel-releasing intrauterine system (LNG IUS) results in a significant reduction in menstrual blood loss from baseline in heavy menstrual bleeding (HMB) in women, including selected women with fibroids. It appears to be more effective than oral medical therapies and results in better quality of life outcomes. It is not clear whether this translates into improved satisfaction but women appear to be less likely to withdraw from treatment by two years. There is very limited and low-quality evidence that LNG IUS appeared to have similar effectiveness to endometrial ablation methods and quality of life outcomes were similar. LNG IUS is associated with adverse events such as breast or pelvic pain and bloating when compared with other treatments, which are not directly comparable to the adverse events encountered with surgery. Both the LNG IUS and hysterectomy improved health-related quality of life, which was most apparent within the five years after treatment. Although many women treated with LNG IUS eventually had hysterectomy (up to 46% within 10 years), the LNG IUS remained cost effective.

Implications for research

Further research is required to compare specific types of endometrial destruction techniques with the LNG IUS. Trials should plan for long-term follow-up (at least five years which is the licensed life span of LNG IUS for contraception) and should focus on measuring satisfaction, and acceptability of the treatment options and quality of life of women with HMB.

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REFERENCES

References to studies included in this review

Barrington 2003 *{published data only}*
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, Gynecology and Reproductive Biology* 2003;**108**:72–4.

Cameron 1987 *{published data only}*
Cameron IT. Dysfunctional uterine bleeding. *Bailliere's Clinical Obstetrics and Gynaecology* 1989;**3**(2):315–27.
* 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**(1):99–110.

Crosignani 1997 *{published data only}*
Crosignani PG, Vercellini P, Mosconi P, Oldani S, Cortesi I, De Giorgi O. Levonorgestrel-releasing intrauterine device versus hysteroscopic endometrial resection in treatment of dysfunctional uterine bleeding. *Obstetrics and Gynecology Clinics of North America* 1997;**90**:257–63.

de Souza 2010 *{published data only}*
Silva-Filho AL, Pereira FAN, de Souza SS, Loures LF, Rocha APC, Valadares CN, et al. Five-year follow-up of

levonorgestrel-releasing intrauterine system versus thermal balloon ablation for the treatment of heavy menstrual bleeding: a randomised controlled trial. *Contraception* 2013;**87**:409–15.
* de Souza SS, Camargos AF, de Rezende CP, Pereira FAN, Araujo CAA, Filho ALS. A randomised prospective trial comparing the levonorgestrel-releasing intrauterine system with thermal balloon ablation for the treatment of heavy menstrual bleeding. *Contraception* 2010;**81**:226–31.

Ergun 2012 ***{published data only}***
Ergun B, Bastu E, Kuru O, Sen S, Kilic Y, Dural O. Comparison of rollerball endometrial ablation and levonorgestrel releasing intrauterine system in the management of abnormal uterine bleeding. *International Journal of Gynecology and Obstetrics* 2012;**119**:S672.
* Ergun B, Kuru O, Sen S, Kilic Y, Bastu E. Rollerball endometrial ablation versus levonorgestrel releasing intrauterine system in the management of abnormal uterine bleeding. *Gineco.ro* 2012;**8**(30):199–201.

Gupta 2013 ***{published data only}***
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.
Sanghera S, Roberts T, Barton P, Daniels J, Middleton L, Gennard L, et al. Cost effectiveness of levonorgestrel intrauterine system for menorrhagia. *BJOG: An International Journal of Obstetrics & Gynaecology* 2013;**120**: 390–1.
Sanghera S, Roberts TE, Barton P, Frew E, Daniels J, Middleton L, et al. Levonorgestrel-releasing intrauterine system vs usual medical treatment for menorrhagia: an economic evaluation alongside a randomised controlled trial. *PLOS One* 2014;**9**(3):e91891.

Hurskainen 2001 ***{published data only}***
Halmesmaki K, Hurskainen R, Teperi J, Grenman S, Kivela A, Kujansuu E, et al. The effect of hysterectomy or levonorgestrel-releasing intrauterine system on sexual functioning among women with menorrhagia: a 5-year randomised controlled trial. *British Journal of Obstetrics and Gynaecology* 2007;**114**:563–8.
Halmesmaki K, Hurskainen R, Tiitinen A, Teperi J, Grenman S, Kivela A, et al. A randomized controlled trial of hysterectomy or levonorgestrel-releasing intrauterine system in the treatment of menorrhagia - effect on FSH levels and menopausal symptoms. *Human Reproduction* 2004;**19**(2): 378–82.
Halmesmaki KH, Hurskainen RA, Paavonen JA, Tuppurainen MT. Randomised controlled trial of the effect of hysterectomy or LNG-IUS use on bone mineral density: a five-year follow up. *Therapy* 2006;**3**:509.
Heliovaara-Peippo S, Halmesmaki K, Hurskainen R, Teperi J, Grenman S, Kivela A, et al. The effect of hysterectomy or levonorgestrel-releasing intrauterine system on lower abdominal pain and back pain among women treated for menorrhagia: a five-year randomised controlled trial. *Acta Obstetricia et Gynecologica* 2009;**88**:1389–96.
Heliovaara-Peippo S, Halmesmaki K, Hurskainen R, Teperi J, Grenman S, Kivela A, et al. The effect of hysterectomy or levonorgestrel-releasing intrauterine system on lower urinary tract symptoms: a 10-year follow-up study of a randomised trial. *British Journal of Obstetrics and Gynaecology* 2010;**117**: 602–9.
Heliovaara-Peippo S, Hurskainen R, Teperi J, Aalto A-M, Grenman S, Halmesmaki K, et al. Quality of life and costs of levonorgestrel-releasing intrauterine system or hysterectomy in the treatment of menorrhagia: a 10 year randomised controlled trial. *Obstetrical and Gynecological Survey* 2014;**69**(4):204–5.
Heliovaara-Peippo S, Hurskainen R, Teperi J, Aalto A-M, Grenman S, Halmesmaki K, et al. Quality of life and costs of levonorgestrel-releasing intrauterine system or hysterectomy in the treatment of menorrhagia: a 10-year randomised controlled trial. *American Journal of Obstetrics and Gynecology* 2013;**209**(6):535.e1–14.
Heliovaara-Peippo S, Oksjoki R, Halmesmaki K, Kaaja R, Teperi J, Grenman S, et al. The effect of hysterectomy or levonorgestrel-releasing intrauterine system on cardiovascular disease risk factors in menorrhagia patients: a 10-year follow-up of a randomised trial. *Maturitas* 2011; **69**:354–8.
Hurskainen R, Teperi J, Aalto A-M, Grenman S, Kivela A, Kujansuu E, et al. Levonorgestrel-releasing intrauterine system or hysterectomy in the treatment of essential menorrhagia: predictors of outcome. *Acta Obstetrica et Gynecologica Scandinavica* 2004;**83**:401–3.
Hurskainen R, Teperi J, Rissanen P, Aalto A-M, Grenman S, Kivela A, et al. Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia. *JAMA* 2004;**291**:1456–63.
* Hurskainen R, Teperi J, Rissanen P, Aalto A-M, Grenman S, Kivela A, et al. Quality of life and cost-effectiveness of levonorgestrel-releasing intrauterine system versus hysterectomy for treatment of menorrhagia: a randomised trial. *Lancet* 2001;**357**:273–7.
Inki P, Hurskainen R, Palo P, Ekholm E, Grenman S, Kivela A, et al. Comparison of ovarian cyst formation in women using the levonorgestrel-releasing intrauterine system versus hysterectomy. *Ultrasound in Obstetrics & Gynecology* 2002; **20**:381–5.
Leminen H, Heliovaara-Peippo S, Halmesmaki K, Teperi J, Grenman S, Kivela A, et al. The effect of hysterectomy or levonorgestrel-releasing intrauterine system on premenstrual symptoms in women treated for menorrhagia: secondary analysis of a randomised controlled trial. *Acta Obstetricia et Gynecologica Scandinavica* 2012;**91**(3):318–325.

Irvine 1998 ***{published data only}***
Irvine GA, Campbell-Brown MB, Lumsden MA, Heikkila A, Walker JJ, Cameron IT. Randomised comparative trial of the levonorgestrel intrauterine system and norethisterone for the treatment of idiopathic menorrhagia. *British Journal of Obstetrics and Gynaecology* 1998;**105**:592–8.

Kaunitz 2010 *{published data only}*

Kaunitz AM, Bissonnette F, Monteiro I, Lukkari-Lax E, DeSanctis Y, Jensen J. Levonorgestrel-releasing intrauterine system for heavy menstrual bleeding improves hemoglobin and ferritin levels. *Contraception* 2012;**86**(5):452–7.

* 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**(3):625–32.

Kilic 2009 *{published data only}*

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.

Kittelsen 1998 *{published data only}*

Istre O, Trolle B. Treatment of menorrhagia with the levonorgestrel intrauterine system versus endometrial resection. *Fertility and Sterility* 2001;**76**(2):304–9.

* 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.

Rauramo I, Elo I, Istre O. Long-term treatment of menorrhagia with levonorgestrel intrauterine system versus endometrial resection. *Obstetrics and Gynecology Clinics of North America* 2004;**104**:1314–21.

Malak 2006 *{published data only}*

Malak KA, Shawki O. Management of menorrhagia with the levonorgestrel intrauterine system versus endometrial resection. *Gynecological Surgery* 2006;**3**:275–80.

Ozdegirmenci 2011 *{published data only}*

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.

Reid 2005 *{published data only}*

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 measurements. *British Journal of Obstetrics and Gynaecology* 2005;**112**:1121–5.

Sayed 2011 *{published data only}*

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.

Sesti 2012 *{published data only}*

Sesti F, Piancatelli R, Pietropoli A, Ruggeri V, Piccione E. Levonorgestrel-releasing intrauterine system versus laparoscopic supracervical hysterectomy for the treatment of heavy menstrual bleeding: a randomised study. *Journal of Women's Health* 2012;**21**(8):851–7.

Shabaan 2011 *{published data only}*

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 randomised clinical trial. *Contraception* 2011;**83**:48–54.

Shaw 2007 *{published data only}*

Shaw RW, Symonds IM, Tamizian O. Randomised comparative trial of thermal balloon ablaion (TBA) v levonorgestrel intrauterine system (LNG IUS) in idiopathic menorrhagia. *XVIII FIGO World Congress of Gynecology and Obstetrics* 2006;**4**:119.

* Shaw RW, Symonds IM, Tamizian O, Chaplain J, Mukhopadhyay S. Randomised comparative trial of thermal balloon ablation and levonorgestrel intrauterine system in patients with idiopathic menorrhagia. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2007;**47**: 335–340.

Soysal 2002 *{published data only}*

Soysal M, Soysal S, Ozer S. A randomized controlled trial of levonorgestrel releasing IUD and thermal balloon ablation in the treatment of menorrhagia. *Zentralblatt Gynakologie* 2002;**124**:213–9.

TALIS 2006 *{published data only}*

Brown PM, Farquhar CM, Lethaby A, Sadler LC, Johnson NP. Cost-effectiveness analysis of levonorgestrel intrauterine system and thermal balloon ablation for heavy menstrual bleeding. *BJOG: An International Journal of Obstetrics & Gynaecology* 2006;**113**:797–803.

* 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 & Gynaecology* 2006;**113**: 257–63.

Tam 2006 *{published data only}*

Tam WH, Yuen PM, Ng DPS, Leung PL, Lok IH, Rogers MS. Health status fuction after treatment with thermal balloon ablation and levonorgestrel intrauterine system for idiopathic menorrhagia: a randomised study. *Gynecologic and Obstetric Investigation* 2006;**62**:84–8.

References to studies excluded from this review

Abu Hashim 2013 *{published data only}*

Abu Hashim H, Zayed A, Ghayaty E, El Rakhawy M. LNG-IUS treatment of non-atypical endometrial hyperplasia in perimenopausal women: a randomised controlled trial. *Journal of Gynecologic Oncology* 2013;**24**(2):128–34.

Endrikat 2009 *{published data only}*

Endrikat J, Shapiro H, Lukkari-Lax E, Kunz M, Schmidt W, Fortier M. A Canadian multicentre study comparing the 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.

Ghazizadeh 2011 ***{published data only}***

Ghazizadeh S, Bakhtiari F, Rahmanpour H, Davari-Tanha F, Ramezanzadeh F. A randomised clinical trial to compare levonorgestrel-releasing intrauterine system (Mirena) vs transcervical endometrial resection for treatment of menorrhagia. *International Journal of Womens Health* 2011; **3**:207–11.

Gupta 2006 ***{published data only}***

Gupta B, Mittal S, Misra R, Deka D, Dadhwal V. Levonorgestrel-releasing intrauterine system vs transcervical endometrial resection for dysfunctional uterine bleeding. *International Journal of Gynecology and Obstetrics* 2006;**95**: 261–6.

Janssen 1999 ***{published data only}***

Janssen CAH. Menorrhagia and the 3-keto-desogestrel-copper medicated intrauterine device. *European Journal of Obstetrics, Gynecology and Reproductive Biology* 1999;**85**: 135–6.

Karacaoglu 2001 ***{published data only}***

Karacaoglu U, Cebi Z, Savan K, Yasar L, Cankaya A, Kupelioglu L, et al. Comparing hysteroscopic ablation with levonorgestrel-releasing intrauterine device in abnormal uterine bleeding cases. *Jinekoloji Ve Obstetrik Dergisi* 2001; **15**(3):172–5.

Karimi-Zarchi 2013 ***{published data only}***

Karimi-Zarchi M, Dehghani-Firoozabadi R, Tabatabaie A, Dehghani-Firoozabadi Z, Teimoori S, Chiti Z, et al. A comparison of the effect of levonorgestrel IUD with oral medroxyprogesterone acetate on abnormal uterine bleeding with simple endometrial hyperplasia and fertility preservation. *Clinical and Experimental Obstetrics and Gynecology* 2013;**40**(3):421–4.

Kucuk 2008 ***{published data only}***

Kucuk U, Ertan K. Continuous oral or intramuscular medroxyprogesterone acetate versus the levonorgestrel releasing intrauterine system in the treatment of perimenopausal menorrhagia: a randomised prospective controlled trial in female smokers. *Clinical Experimental Obstetrics and Gynecology* 2008;**35**(1):57–60.

Lahteenmaki 1998 ***{published data only}***

Lahteenmaki P, Haukkamaa M, Puolakka J, Riikonen U, Sainio S, Suvisaari J, et al. Open randomised study of use of levonorgestrel releasing intrauterine system as alternative to hysterectomy. *BMJ* 1998;**316**:1122–6.

Lee 2013 ***{published data only}***

* Lee BS, Ling X, Asif S, Kraemer P, Hanisch JU, Inki P. Levonorgestrel-releasing intrauterine system versus conventional medical therapy for heavy menstrual bleeding in the Asia-Pacific region. *International Journal of Gynecology and Obstetrics* 2013;**121**:24–30.

Xu L, Lee BS, Asif S, Kraemer P, Inki P. Satisfaction and health-related quality of life in women with heavy menstrual bleeding; results from a non interventional trial of the levonorgestrel-releasing intrauterine system or conventional medical therapy. *International Journal of Women's Health* 2014;**6**:547–54.

Milsom 1991 ***{published data only}***

Milsom I, Andersson K, Andersch B, Rybo G. A comparison of flurbiprofen, tranexamic acid and a levonorgestrel-releasing intrauterine contraceptive device in the treatment of idiopathic menorrhagia. *American Journal of Obstetrics and Gynecology* 1991;**164**:879–83.

Rogerson 1999 ***{unpublished data only}***

Rogerson L, Crocombe W, Duffy S. SMART - Satisfaction with Mirena and ablation: a randomised trial (abstract). British Society of Gynaecological Endocrinology. 1999.

Romer 2000 ***{published data only}***

Romer T. Prospective comparison study of levonorgestrel IUD versus Roller-Ball endometrial ablation in the management of refractory recurrent hypermenorrhea. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2000;**90**:27–9.

Tosun 2014 ***{published data only}***

Tosun AK, Tosun I, Suer N. Comparison of levonorgestrel-releasing intrauterine device with oral progestins in heavy menstrual bleeding (HMB) cases with uterine leiomyoma (LNG-IUD and oral progestin usage in myoma uteri). *Pakistan Journal of Medical Sciences* 2014;**30**(4):834–9.

References to studies awaiting assessment

Ghazizadeh 2014 ***{published data only}***

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 randomised clinical trial. *Journal of Gynecologic Surgery* 2014;**30**(4):215–8.

McMillan 1998 ***{unpublished data only}***

McMillan L. Randomised controlled study comparing the efficacy of Levonorgestrel intrauterine device with Nd:YAG laser endometrial ablation for the treatment of menorrhagia and premenstrual syndrome. National Research Register, id N0080056736.

McMillan 2005 ***{published data only}***

McMillan L. Randomised controlled study comparing the efficacy of levonorgestrel intrauterine device with surgical treatment of menorrhagia by total endometrial ablation. National Research Register, id N0080056730.

References to ongoing studies

Abdel-Alim 2003 ***{unpublished data only}***

Abdel-Alim S A-R. Evaluation of the role of levonorgestrel releasing intrauterine system in management of menorrhagia. Email contact.

Herman 2013 ***{published data only}***

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. *BMC Women's Health* 2013;**13**:32.

SHiPP 2013 ***{unpublished data only}***

SHiPP (Stopping Heavy Periods Project), Identifier NCT02002260. Ongoing study February 2013 – estimated completion date January 2017.

Additional references

Andersson 1994

Andersson K, Odlind V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: a randomized comparative trial. *Contraception* 1994; **49**:56–72.

Baldwin 2013

Baldwin MK, Jensen JT. Contraception during the perimenopause. *Maturitas* 2013;**76**(3):235–42.

Berqvist 1983

Berqvist A, Rybo G. Treatment of menorrhagia with intrauterine release of progesterone. *British Journal of Obstetrics and Gynaecology* 1983;**90**:255–8.

Chimbira 1980

Chimbira TH, Anderson ABM, Turnbull AC. Relation between measured menstrual blood loss and patient's subjective assessment of loss, duration of bleeding, number of sanitary towels used, uterine weight and endometrial surface area.. *British Journal of Obstetrics and Gynaecology* 1980;**87**:603–9.

Clegg 2007

Clegg JP, Guest JF, Hurskainen R. Cost-utility of levonorgestrel intrauterine system compared with hysterectomy and second generation endometrial ablative techniques in managing patients with menorrhagia in the UK. *Current Medical Research and Opinions* 2007;**23**(7): 1637–48.

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**:939–49.

Coulter 1995

Coulter A, Kelland J, Peto V, Rees MCP. Treating menorrhagia in primary care. *International Journal of Technology Assessment in Health Care* 1995;**11**(3):456–71.

Farquhar 1996

Farquhar CM, Kimble R. How do NZ gynaecologists treat menorrhagia?. *Australian and New Zealand Journal of Obstetrics & Gynaecology* 1996;**36**(4):1–4.

Farquhar 2002

Farquhar C, Steiner C. Hysterectomy rates in the United States 1990-1997. *Obstetrics and Gynecology* 2002;**99**: 229–34.

Fergusson 2013

Fergusson RJ, Lethaby A, Shepperd S, Farquhar C. Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews* 2013, Issue 11. [DOI: 10.1002/14651858.CD000329.pub2]

Fraser 2009

Fraser IS, Langham S, Uhl-Hochgraeber K. Health-related quality of life and economic burden of abnormal uterine bleeding. *Expert Review of Obstetrics and Gynecology* 2009; **4**:179–89.

Ganz 2013

Ganz ML, Shah D, Gidwani R, Filonenko A, Su W, Pocoski J, et al. The cost effectiveness of the levonorgestrel-releasing intrauterine system for the treatment of idiopathic heavy menstrual bleeding in the United States. *Value in Health* 2013;**16**:325–33.

Hallberg 1966

Hallberg L, Hogahl AM, Nilsson L, Rybo G. Menstrual blood loss - a population study. *Acta Obstetricia et Gynecologica Scandinavica* 1966;**45**:320–51.

Higgins 2011

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.

Higham 1990

Higham JM, O'Brien PMS, Shaw RW. Assessment of menstrual blood using a pictorial chart. *British Journal of Obstetrics and Gynaecology* 1990;**97**:734–9.

Inki 2007

Inki P. Long-term use of the levonorgestrel-releasing intrauterine system. *Contraception* 2007;**75**(Suppl 6): S161–S166.

Kaunitz 2009

Kaunitz AM, Meredith S, Inki P, Kubba A, Sanchez-Ramos L. Levonorgestrel-releasing intrauterine system and endometrial ablation in heavy menstrual bleeding: a systematic review and meta-analysis. *Obstetrics and Gynecology* 2009;**113**:1104–16.

Kaunitz 2012

Kaunitz AM, Inki P. The levonorgestrel-releasing intrauterine system in heavy menstrual bleeding. *Drugs* 2012;**72**(2):193–215.

Liu 2007

Liu Z, Doan QV, Blumenthal P, Dubois RW. A systematic review evaluating health-related quality of life, work impairment, and health-care costs and utilisation in abnormal uterine bleeding. *Value Health* 2007;**10**:183–94.

Mansour 2007

Mansour D. Modern management of abnormal uterine bleeding - the levonorgestrel intrauterine system. *Best Practice Research in Clinical Obstetrics and Gynecology* 2007; **21**:1007–21.

Matteson 2013

Matteson KA, Rahn DD, Wheeler TL, Casiano E, Siddiqui NY, Harvie HS, et al. Nonsurgical management of heavy menstrual bleeding: a systematic review. *Obstetrics and Gynecology* 2013;**121**(3):632–43.

Middleton 2010
Middleton LJ, Champaneria R, Daniels JP, Bhattacharya S, Cooper KG, Hilken NH, et al. Hysterectomy, endometrial destruction and levonorgestrel releasing intrauterine system (Mirena) for heavy menstrual bleeding: systematic review and meta-analysis of data from individual patients. *BMJ* 2010;**341**:c3929.

Moragianni 2007
Moragianni VA, Somkuti SG. Profound hypothyroidism-induced acute menorrhagia resulting in life-threatening anemia. *Obstetrics and Gynecology* 2007;**110**(2 Pt 2):515–7.

NICE 2007
National Insititute for Care and Excellence. Heavy menstrual bleeding. NICE Clinical Guideline 44. guidance.nice.org.uk/cg44 January 2007.

Nilsson 1978
Nilsson CG, Luukkainen T, Arko H. Endometrial morphology of women using a d-norgestrel-releasing intrauterine device. *Fertility and Sterility* 1978;**29**:397–401.

Reid 2005b
Reid PC, Mukri F. Trends in number of hysterectomies performed in England for menorrhagia: examination of health episode statistics 1989 to 2002-3. *BMJ* 2005;**330**: 938–9.

Roberts 2011
Roberts TE, Tsourapas A, Middleton LJ, Champaneria R, Daniels JP, Cooper KG, et al. Hysterectomy, endometrial ablation and levonorgestrel releasing intrauterine system (Mirean) for treatment of heavy menstrual bleeding: cost effectiveness analysis. *BMJ* 2011;**342**:d2202.

Rodriguez 2010
Rodriguez MI, Darney PD. Non-contraceptive applications of the levonorgestrel intrauterine system. *International Journal of Womens' Health* 2010;**2**:63–8.

Shapley 2004
Shapley M, Jordan K, Croft PR. An epidemiological survey of symptoms of menstrual loss in the community. *British Journal of General Practice* 2004;**54**:359–64.

Somboonporn 2011
Somboonporn W, Panna S, Temtanakitpaisan T, Kaewrudee S, Soontrapa S. Effects of the levonorgestrel-releasing intrauterine system plus estrogen therapy in perimenopausal and postmenopausal women: systematic review and meta-analysis. *Menopause* 2011;**18**(10):1060–6.

Suvisaari 1996
Suvisaari J, Lahteenmaki P. Detailed analysis of menstrual bleeding patterns after postmenstrual and postabortal insertion of a copper IUD or a levonorgestrel-releasing intrauterine system. *Contraception* 1996;**54**:201–8.

Wright 2013
Wright JD, Herzog TJ, Tsui J, Ananth CV, Lewin SM, Lu Y-S, et al. Nationwide trends in the performance of inpatient hysterectomy in the United States. *Obstetrics and Gynecology* 2013;**122**(2):233–41.

Xu 2014
Xu L, Lee BS, Asif S, Kraemer P, Inki P. Satisfaction and health-related quality of life in women with heavy menstrual bleeding; results from a non interventional trial of the levonorgestrel-releasing intrauterine system or conventional medical therapy. *International Journal of Women's Health* 2014;**6**:547–54.

You 2006
You JH, Sahota DS, MoYuen P. A cost utility analysis of hysterectomy, endometriation resection and ablation and medical therapy for menorrhagia. *Human Reproduction* 2006;**21**:1878–83.

References to other published versions of this review

Lethaby 1999
Lethaby AE, Cooke I, Rees M. Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews* 1999, Issue 4. [DOI: 10.1002/14651858.CD002126]

Lethaby 2005
Lethaby A, Cooke I, Rees MC. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [DOI: 10.1002/14651858.CD002126.pub2]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Barrington 2003

Methods	Parallel group study in single centre No of women randomised: 50 Dropouts: at 6 months 4/25 (16%) in LNG IUS group and 2/25 (8%) in ablation group No of women analysed: 44 No power calculation or ITT analysis Source of funding not stated
Participants	Country: UK Women with menorrhagia refractory to medical treatment referred by GPs to gynaecology clinic in district hospital. Exclusion: Cavity > 12 cm; subserous fibroids; malignant or pre-malignant pathology (from endometrial biopsy)
Interventions	(1) Levonorgestrel-releasing intrauterine system (LNG IUS, Mirena) (2) Thermal balloon ablation after pre-operative endometrial thinning with gosarelin one month prior Duration: 6 months
Outcomes	• PBAC score at 6 months • Improvement in bleeding • Requirement for further treatment (surgical)
Notes	Preoperative menstrual bleeding was higher in the thermal balloon group compared to the LNG IUS group (P value 0.02)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Highly unlikely
Blinding of outcome assessment (detection bias) All outcomes	High risk	Highly unlikely

Barrington 2003 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All women received their allocated treatment. 44/50 analysed for primary outcome at 6 months. Reasons for withdrawal/ dropout given, however because women in LNG IUS group were able to request removal of the device for inefficacy, this could have caused bias (women having hysterectomy not able to "withdraw" for this reason)
Selective reporting (reporting bias)	Unclear risk	Outcomes not clearly specified
Other bias	High risk	Preoperative menstrual bleeding was significantly higher in the thermal balloon group compared to the LNG IUS group. Bias is likely as menstrual bleeding was measured postoperatively without adjustment for higher scores

Cameron 1987

Methods	Single centre, parallel group design with no blinding. Number of participants randomised: n = 30. Number of participants analysed: n = 23 (2, 2, 2 and 1 were lost from the danazol, mefenamic acid, norethisterone and progestogen coil groups respectively). No power calculation or ITT analysis. Source of funding, Birthright Research Grant, RCOG.
Participants	Country: UK Women, aged between 29 and 50, recruited from Royal Infirmary, Edinburgh. Inclusion criteria: menstrual blood loss > 50 mL/cycle. No exclusion criteria stated.
Interventions	1) Norethisterone, 5 mg twice daily, days 15-25 of cycle. 2) Danazol, 200 mg, daily. 3) Mefenamic acid, 500 mg three times a day, for first 5 days of menstruation. 4) Progesterone-releasing IUS, 65 ug progesterone daily. Duration: 2 cycles.
Outcomes	• Menstrual blood loss (alkaline haematin method). • Duration of menstruation (days).
Notes	Groups not comparable at baseline. Baseline menstrual blood loss in danazol group significantly greater than in mefenamic acid and progesterone IUS groups. Original data not available from principal author; HMB data reported as median and range. Median substituted for mean in meta-analysis and standard deviation estimated from the range

Cameron 1987 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Highly unlikely
Blinding of outcome assessment (detection bias) All outcomes	High risk	Highly unlikely
Incomplete outcome data (attrition bias) All outcomes	High risk	Substantial dropout (7/30 (23%)) - no reasons given
Selective reporting (reporting bias)	Unclear risk	Adverse events not reported
Other bias	High risk	Substantial imbalance in menstrual blood loss at baseline between groups - as this is the primary outcome, the estimates are likely to be biased

Crosignani 1997

Methods	Parallel group, single centre RCT. No of women randomised: 70 No of women analysed: 69 Exclusions post randomisation: 0. Losses to follow-up: 6 months = 0, 12 months = 1. Power calculation for sample size was performed and analysis was by ITT Funding was partially supported by the Italian National Research Council and Leiras Pharmaceuticals provided the intrauterine devices
Participants	Country: Italy Aged 38-53 years, all referred for a hysterectomy because of heavy menstrual bleeding Inclusion criteria: > 80 mL/cycle loss (as measured by > 100 points on pictorial charts) . Negative smear within 12 months. Endometrial pathology excluded by transvaginal ultrasound, diagnostic hysteroscopy and endometrial biopsy. Uterine size less than 8 weeks. Exclusion criteria: Abnormal uterine cavity, fibroids greater than 3 cm, or atypical hyperplasia. Pregnancy, breast feeding or uncertainty about future fertility. Recent use of oestrogens or progestogens (within 3 months), GnRH (within 6 months), any medication affecting menstrual blood loss, concomitant illness, Hb < 10 g/dL

Crosignani 1997 (*Continued*)

Interventions	(1) Levonorgestrel-releasing (20 ug/day) intrauterine contraceptive system inserted within seven days of menstruation (2) Endometrial resection in the early proliferative phase using a rollerball and a 90 degree loop. All the resections were performed by the same surgeon Duration: 12 months. Follow-up assessments at 6 and 12 months
Outcomes	• Menstrual blood loss by PBAC at 6 and 12 months follow-up • Hb and serum Fe at 6 and 12 months • Participant satisfaction (very satisfied, satisfied, uncertain, dissatisfied) • Quality of life (International Quality of Life Assessment Short Form 36 Italian version, release 1.6) • Proportion of women with amenorrhoea at 12 months • Proportion of women with side effects
Notes	The Academic Department undertaking the study was specifically interested in hysteroscopic surgery and hence the endometrial resection results may be better than those applicable to the general population of clinicians

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomisation sequence"
Allocation concealment (selection bias)	Low risk	"consecutively numbered opaque sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	For primary outcome of menstrual bleeding, 1/70 not included in the analysis. For analysis of PBAC scores, 10/70 not included (5 from each group) and for analysis of quality of life, 8/70 not included (4 in each group). Reasons for attrition were given
Selective reporting (reporting bias)	Low risk	Outcomes clearly specified and reported
Other bias	Low risk	No evidence of an imbalance between groups at baseline

de Souza 2010

Methods	Parallel group RCT, single centre No of women randomised: 58 No of women analysed: At 12 months, 55 (1 woman in Mirena group and 2 women in balloon group required hysterectomy). At 5 years, 52 (1 woman required hysterectomy and 3 were lost to follow-up in Mirena group but 27/30 were analysed; 6 women required hysterectomy and 3 were lost to follow-up in balloon group but 25/28 were analysed) Power calculation for sample size: difference of > 40% between proportions, but this calculation did not allow for dropouts ITT analysis but did not take into account dropouts Funding: Bayer provided the materials used in the study (both interventions)
Participants	Country: Brazil Women recruited between January 2005 and March 2007, with mean age 42 and 44 years and baseline PBAC 542 and 420 Inclusion criteria: 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, 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 also required to have completed their families Exclusion criteria: not reported
Interventions	(1) Levonorgestrel-releasing IUS (Mirena) (2) Thermal balloon ablation (Thermachoice) under general anaesthesia Both procedures initiated during the first 15 days of a menstrual cycle
Outcomes	• 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 Assessed at 1, 6 and 12 months after the procedures and additionally at 5 years
Notes	Two publications - one assessed outcomes at 12 months and the other at 5 years after treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated randomisation list"
Allocation concealment (selection bias)	Unclear risk	Not reported

de Souza 2010 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	At 12-month assessment, minimal drop-outs but at 5 years assessment only 17/30 in Mirena group and 11/28 in balloon group were still premenopausal and evaluated for Hb, quality of life scores and bleeding pattern
Selective reporting (reporting bias)	Unclear risk	Adverse events not prespecified or reported
Other bias	Low risk	Groups appeared comparable at baseline

Ergun 2012

Methods	Single centre parallel group RCT No of women randomised: 58 No of women analysed: 42 (reasons for dropouts not given) No ITT analysis or power calculation for sample size Funding: not reported
Participants	Country: Turkey Women with abnormal uterine bleeding which had not responded to medical treatment Inclusion criteria: > 35 years of age, regular menstrual cycle, score of 100 on PBAC Exclusion criteria: ongoing pregnancy, pelvic infection, abnormality in the uterus, uterine cavity and/or suspicious endometrial histology (screened by TVUS), abnormal cervical or endometrial histology, pathology that might require a hysterectomy, contraindication to administration of anaesthetic agents, desire to preserve fertility
Interventions	1. LNG IUS inserted within first 15 days of menstrual cycle 2. Rollerball endometrial ablation undertaken by obstetrics and gynaecology specialist Duration: 12 months
Outcomes	• PBAC scores • Further surgical treatment • Failure of treatment • Amenorrhoea and hypomenorrhoea • Satisfaction • Hb levels
Notes	

Ergun 2012 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated 'random' but no method described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Substantial dropout and no reasons given
Selective reporting (reporting bias)	Unclear risk	Outcomes not clearly prespecified
Other bias	Unclear risk	Characteristics of randomised participants not reported, so not clear if groups were comparable at baseline. Unequal numbers in randomised groups

Gupta 2013

Methods	Parallel group RCT, multicentre (n = 63 in UK) No of women randomised: 571 No of women analysed: At 2 years, 231 in medical treatment group and 247 in LNG IUS group but sensitivity analysis with imputation of missing data was undertaken Power calculation for sample size: 90% power to detect small to moderate (0.3 SD) differences in primary outcome at any one time point - allowed for 20% dropout ITT analysis Funding: NIHR Health Technology Assessment Program
Participants	Country: UK Mean age: 42 years Inclusion criteria: aged between 25 and 50 years, presenting to primary care physicians with menorrhagia involving at least 3 consecutive menstrual cycles Exclusion criteria: intention to become pregnant over the next 5 years, taking hormone therapy or tamoxifen, intermenstrual bleeding, post coital bleeding, findings suggestive of fibroids or other disorders, contraindications to or a preference for either the LNG IUS or usual medical treatments, heavy irregular bleeding

Gupta 2013 (*Continued*)

Interventions	(1) Levonorgestrel-releasing IUS (2) Usual medical treatment (mefenamic acid, tranexamic acid, norethindrone, combined oestrogen-progestogen or progesterone-only oral contraceptive pill, medroxyprogesterone acetate injection, chosen by the physician and patient according to contraceptive needs and desire to avoid hormone therapy) Women are permitted to change treatments, as well as between groups or could discontinue treatment - to replicate usual practice Duration: 6 months, 2, 5 and 10 years
Outcomes	Primary: • Patient reported score on the Menorrhagia Multi-Attribute Scale (MMAS) Secondary: • General health-related quality of life (measured on SF36, EQ-5D descriptive system and EQ-5D visual analogue scale • Sexual activity scale (Sexual Activity Questionnaire) • Further requirement for surgery • Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computerised minimised randomisation procedure"
Allocation concealment (selection bias)	Low risk	"assigned by telephone or web based central randomisation service" at clinical trials unit in University of Birmingham
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clear explanations given for missing data and sensitivity analyses performed where values were imputed for missing data
Selective reporting (reporting bias)	Low risk	Clear and comprehensive protocol
Other bias	Low risk	Groups comparable at baseline

Hurskainen 2001

Methods	Multicentre (n = 5), parallel group study. No of women randomised: 236 No of women analysed: 228 at 12 months, 232 at 5 years, 221 at 10 years Dropouts: LNG IUS group: 1.6% at 6 months and 2.5% at 12 months follow-up; hysterectomy group: 9.4% at 6 months and 4.3% at 12 months follow-up. Power calculation for sample size and ITT analysis. Source of funding: Academy of Finland, STAKES and research funds of the University Hospitals in Finland. Mirena was provided free of charge by Leiras
Participants	Country: Finland Women, aged 35 to 49 (mean age 43) referred by GPs or gynaecologists to 5 university hospitals. Inclusion criteria: menorrhagia, still menstruating, family completed, eligible for hysterectomy Exclusion criteria: submucous fibroids; endometrial polyps; ovarian tumours or cysts; cervical disease; urinary or bowel symptoms or pain due to fibroids; lack of indication for hysterectomy; history of cancer; menopause; severe depression; metrorrhagia as main complaint; previous treatment failure with LNG IUS; severe acne; uterine malformation
Interventions	1. LNG IUS 2. Hysterectomy (either abdominal, vaginal or laparoscopy)
Outcomes	Primary: • Quality of life measured by EQ-5D Secondary: • Quality of life measured by Rand 36, Anxiety scale, Becks depression scale, McCoy sex scale • Costs • Hospital services (operations, inpatient days, procedures, outpatient visits) • Menstrual blood loss (measured by alkaline haematin method) • Satisfaction • Adverse effects (urinary symptoms, bone mineral density, cardiovascular risk factors, ovarian cysts, lower abdominal pain, back pain)
Notes	Results analysed at 1, 5 and 10 years follow-up.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation stratified by centre in clusters by drawing from a hat
Allocation concealment (selection bias)	Low risk	"numbered opaque sealed envelopes" - physicians and other study personnel did not participate in allocation execution

Hurskainen 2001 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal dropouts at 12 months (3/119 (2. 5%) in LNG group and 5/117 (4.3%) in hysterectomy group). At 5-year follow-up, 2/119 (1.7%) lost to follow-up in LNG group and 2/117 (1.7%) lost to follow-up in hysterectomy group
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Groups appeared similar at baseline

Irvine 1998

Methods	Parallel group, single centre RCT. No of women randomised: 44 No of women analysed: 36 Exclusions post randomisation: 0. Withdrawal from treatment: 3 months (2 from LNG group and 6 from Norethisterone group) Power calculation for sample size was performed . Both ITT (for primary outcome) and per protocol analysis performed. Source of funding not stated.
Participants	Country: UK Women aged 18-45 years all referred to specialist clinic complaining of regular heavy menstrual bleeding. 151 women were screened but 197 were excluded from eligibility (41 measured menstrual blood loss < 80 mL, 62 declined to do menstrual blood loss measurements, 4 declined to participate) Inclusion criteria: > 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. Exclusion criteria: abnormal pelvic examination, recent use of oestrogens, progestogens or anticoagulants (within 3 months), injectable hormones for contraception (within 12 months)
Interventions	(1) Levonorgestrel-releasing (20 ug/day) intrauterine contraceptive system inserted within seven days of menstruation (2) Norethisterone 5 mg three times daily taken on Day 5-26 of the menstrual cycle for three cycles Duration: 3 months

Irvine 1998 (*Continued*)

Outcomes	Primary: • Menstrual blood loss (alkaline haematin method) at 3 months follow-up Secondary: • Hb and serum Fe at pretreatment and 3 months (or sooner if premature termination) • Participant symptom/side effect questionnaire at pretreatment, 1 and 3 months • Participant satisfaction categorised as liking treatment very well, well, moderately, poorly. • Women were asked how their periods interfered with their quality of life both before and after treatment. • Proportion of women with amenorrhoea • Proportion of women with specified side effects • Withdrawal from treatment because of adverse events relating to treatment • Acceptability of treatment (willingness to continue).
Notes	Outcomes assessed at three months which is relatively short period to assess the effectiveness of the LNG IUS. Power calculation performed prior to commencement of trial to assess group size and ITT analysis of data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated"
Allocation concealment (selection bias)	Low risk	"sealed opaque consecutively numbered envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors stated that both ITT and per protocol analyses were performed but it appears that this was only for menstrual blood loss and satisfaction. Per protocol analyses were undertaken for all other outcomes. Completers of the trial at 3 months were 20/22 (90.9%) in LNG group and 16/22 (72.7%) in NET group. Side effects were collected in only 12/22 (54.5%) of NET group

Irvine 1998 (*Continued*)

Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Groups appeared similar at baseline

Kaunitz 2010

Methods	Multicentre (n = 55), parallel group RCT No of women randomised: 165 No of women analysed: 165 for absolute change and 160 for treatment success ITT analysis and use of last observation carried forward for dropouts Power calculation for sample size: allowed for 20% dropouts, 69 women per treatment group to detect a significant difference in HMB between groups (83% reduction with LNG IUS and 50% reduction with MPA) (90% power) and 40% difference in proportions with successful treatment (99% power) Funding: Bayer Schering Pharma AG
Participants	Country: USA, Canada and Brazil Women with mean age 38 or 39 years Inclusion criteria: parous women aged 18 years or more with idiopathic heavy menstrual bleeding (menstrual blood loss >/= 80 mL per cycle (assessed by alkaline haematin method) desiring intrauterine contraception and willing to use barrier contraception Exclusion criteria: changes in menstrual irregularity, 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, body mass index > 35k g/m^2
Interventions	1. LNG IUS (placed within 7 days of the onset of menstruation) (only 1 attempt at replacement could be made) 2. Medroxyprogesterone acetate (MPA) 10mg once per day for 10 consecutive days of the cycle starting on day
Outcomes	Primary: • 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) Secondary: • Adverse events Follow-up at 3 and 6 months.
Notes	Screening phase for 2 to 3 menstrual cycles to assess baseline HMB (alkaline haematin method). Two publications: HMB outcomes assessed at 6 months and Hb and ferritin levels at 6 months. At the end of the study, women assigned to MPA were able to choose to use a LNG IUS and those allocated to LNG IUS were allowed to continue its use

Kaunitz 2010 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"centralised interactive voice system" with "random permuted block lengths of 4 to attain balance within the strata and by country"
Allocation concealment (selection bias)	Low risk	Centralised system of allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal dropouts and analysis by ITT and last observation carried forward
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Groups appeared similar at baseline

Kilic 2009

Methods	Single centre, parallel group RCT No of women randomised: 40 No of women analysed: 40 Power calculation for sample size: 9 per group for 80% power to detect a 20% decrease in the PBAC score with SD 14 ITT analysis Funding: not stated
Participants	Country: Turkey Women taking anticoagulant therapy after cardiac valve replacement, with median age 36 years Inclusion criteria: women with a complaint of HMB and PBAC score > 185 Exclusion criteria: not reported
Interventions	1. LNG IUS inserted during the first 3 days of menstrual bleeding - antibiotic prophylaxis used 2. Control - observation

Kilic 2009 (*Continued*)

Outcomes	Primary: • Menstrual blood loss (measured by PBAC) Secondary: • Hb, haematocrit and ferritin levels
Notes	HMB is a potential side effect of treatment with anticoagulant therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"simple randomisation method" but this method was not described
Allocation concealment (selection bias)	Unclear risk	"closed envelopes" - insufficient information to know whether allocation was properly concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	"all participants completed the study"
Selective reporting (reporting bias)	Unclear risk	Adverse events not assessed
Other bias	Low risk	Groups appeared comparable at baseline - no other potential bias

Kittelsen 1998

Methods	Single centre, parallel group design Number of women randomised: n = 60 Number of withdrawals: n = 7 (6 in the LNG IUS group because of unwanted adverse events and 1 in the TCRE group because of dislike of treatment option after randomisation) Power analysis for sample size was performed. Analysis was not by ITT. Source of funding: Leiras Finland.
Participants	Country: Norway Inclusion criteria: Premenopausal women aged 30 to 49 years with heavy menstrual bleeding recruited from a gynaecology clinic specialising in operative hysteroscopy.

Kittelsen 1998 (*Continued*)

	Inclusion criteria: premenopausal (FSH > 40 mLU/mL and 17B oestradiol < 0.2 nmol/mL), score of > 100 on PBAC with a regular uterine cavity. Exclusion criteria: hormone treatment in past 3 months, previous history of DVT, thromboembolism 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
Interventions	(1) Levonorgestrel-releasing intrauterine system (LNG IUS) (Mirena) inserted within 7 days of the start of menstruation. (2) Transcervical resection of the endometrium (TCRE) performed regardless of day of menstrual cycle. Duration: 20 months, 3 years.
Outcomes	• PBAC score 12, 24 and 36 months after treatment. • Menstrual pain • Adverse events • Failure of treatment (further surgery or removal of IUS) • Discontinuation from study
Notes	Study has been extended to 36 months.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"random permuted blocks" using a computer code
Allocation concealment (selection bias)	Low risk	"sealed envelopes" opened at entry
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	11/30 (36.7%) in LNG group had discontinued treatment by 36 months. 7/29 (24.1%) in TCRE group discontinued (4 because of treatment failure) in the study by 36 months
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Groups comparable at baseline

Malak 2006

Methods	Single centre parallel group RCT No of women randomised: 60 No of women analysed: 56 (4 patients in the LNG IUS group discontinued treatment) Power calculation for sample size: 30 women per group with 90% power to find a success rate of 85% in LNG IUS group and 70% in endometrial resection group No ITT analysis Funding: not stated
Participants	Country: Egypt Women scheduled to undergo hysterectomy for treatment of excessive uterine bleeding with or without dysmenorrhoea, with mean age 46 and 47 years Inclusion criteria: age between 40 and 50 years, regular uterine cavity < 10 cm in length as measured by ultrasound, no wish for further pregnancy Exclusion criteria: one fibroid > 3cm in diameter or > 3 uterine fibroids as assessed by ultrasonography, history or current clinical evidence or suspicion of malignancy or current liver disease, adnexal tumours or cysts or pelvic inflammatory disease within the previous 12 months
Interventions	Screening period of 2 months prior to enrolment. PBAC score >100 considered excessive bleeding 1. LNG IUS inserted following menstruation 2. Endometrial resection (ER) under general anaesthesia
Outcomes	Primary: • Women's decision to continue treatment (satisfaction) Other outcomes: • Menstrual blood loss - amenorrhoea or hypomenorrhoea, PBAC score at 12 months • Treatment success (defined as PBAC score < 75 at 12 months • Treatment failure (PBAC score > 75, removal of the LNG IUS in the LNG IUS group or resurgery for any reason in the ER group) • Adverse events • Quality of life (EQ VAS score) Follow-up at 6 and 12 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomisation table"
Allocation concealment (selection bias)	Unclear risk	"sealed envelopes" but unclear if sequentially numbered and opaque

Malak 2006 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Minimal dropout (4/30 in LNG IUS group) but none in the ER group
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	There was a significant difference in parity status between the 2 randomised groups

Ozdegirmenci 2011

Methods	Single centre parallel group study No of women randomised: 86 No of women analysed: 75 (11 lost to follow-up from hysterectomy group) Power calculation for sample size: total of 72 participants for 90% power and d = 0.70 effect size. 20% more patients enrolled to allow for loss to follow-up Analysis not by ITT Funding: not stated
Participants	Country: Turkey Women with clinical suspicion of adenomyosis complaining of menorrhagia and/or dysmenorrhoea and with confirmed adenomyosis, with mean age 44 and 46 years Inclusion criteria: not specifically reported - women with adenomyosis by sonogram and MRI Exclusion criteria: endometrial pathology, submucous fibroids, intramural or subserous fibroids > 2 cm, postmenopausal status, pelvic inflammatory disease, 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 All women had menorrhagia.
Interventions	1. LNG IUS 2. Hysterectomy (abdominal)
Outcomes	Primary: • Quality of life (WHO Quality of Life - Short Form, Turkish Version (WHOQOL-BREF TR) at 12 months Other: • Oligomenorrhoea • Side effects • Hb levels

Ozdegirmenci 2011 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated codes"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Substantial lost to follow-up from the hysterectomy group (26%) and none from the LNG IUS group
Selective reporting (reporting bias)	Low risk	Outcomes were clearly specified and reported
Other bias	Low risk	Groups appeared comparable at baseline and no other potential bias

Reid 2005

Methods	Single centre, parallel group study design. Potential for bias because main author was aware of the allocation and measured the outcomes. Number of women randomised and analysed: 51. Number of women who discontinued treatment: 4 in LNG group and 5 in MFA group. Power calculation for sample size performed and ITT analysis. Source of funding: Schering.
Participants	Country: UK Women were either referred by GPs or self referred after ads in the local press. Inclusion criteria: Aged 18 to 47 years; with good general health; regular ovulatory menstrual cycles 21-35 days and HMB measured by alkaline haematin method >/= 80mL. Exclusions: Undiagnosed abnormal bleeding; anovulatory; submucous fibroids or fibroids > 5 cm3 in total volume (US); uterine sound > 10 cm; abnormal cervical cytology; untreated hypertension; abnormal thyroid or liver function tests; asthma; IUCD in situ; previous treatment for menorrhagia; hormonal contraceptives in previous 4 months

Interventions	(1) Levonorgestrel-releasing intrauterine system (2) Mefenamic acid 500 mg 3 times daily for first 4 days of cycle. Duration: 3 cycles and 6 cycles.
Outcomes	Primary: • HMB (measured by alkaline haematin method) • Total menstrual fluid loss (TMFL) • PBAC score.
Notes	The principal author reported a conflict of interest - he had received travel support from Schering. This is the first study to measure TMFL as opposed to menstrual blood loss

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"random permuted blocks"
Allocation concealment (selection bias)	Low risk	"consecutively numbered opaque sealed envelopes" prepared off site
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients lost to follow-up or dropouts included in final analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	The authors did not present a table of baseline characteristics of the participants

Sayed 2011

Methods	Single centre parallel group RCT No of women randomised: 58 No of women analysed: 44 were still in the study at 12 months follow-up but bleeding outcomes measured in substantially fewer because of treatment failure Power calculation for sample size - 29 participants per group (with 15% attrition) for 90% power ITT analysis claimed by authors but missing data not included in analyses Funding: Bayer Schering Pharma (LNG IUS supply), Proctor and Gamble (sanitary pads), Assiut University Egypt (lab work)
Participants	Country: Egypt Participants recruited from outpatient gynaecology clinics of Assiut University, mean age 37 years Inclusion criteria: heavy menstrual bleeding, requested contraception, regular cycle, between 20 and 50 years of age at initial assessment, lived sufficiently close to hospital for follow-up, fibroid(s) detected from pelvic ultrasound Exclusion criteria: pregnancy, history of ectopic pregnancy, puerperal sepsis, pelvic inflammatory disease, evidence of defective coagulation, 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
Interventions	1. LNG IUS 2. Low dose combined oral contraceptive (COC) - 30 ug ethinyl oestradiol and 150 ug levonorgestrel Follow-up at 3, 6, 9 and 12 months
Outcomes	Primary: • Reduction of HMB (%) (PBAC and alkaline haematin assessment) at 12 months Other: • Hb and ferritin levels • Quality of life (HRQoL) • Treatment failure
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated table of random numbers"
Allocation concealment (selection bias)	Low risk	"sealed envelopes" which were opened for allocation with each enrolment

Sayed 2011 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Substantial loss to follow-up and treatment failure - bleeding outcomes only measured in 20/58 (PBAC) and 22/58 (alkaline haematin)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Groups appeared comparable at baseline and no other potential bias

Sesti 2012

Methods	Single centre parallel group RCT No of women randomised: 72 No of women analysed: 72 Power calculation for sample size ITT analysis Funding: not stated
Participants	Country: Italy Participants were women with HMB unresponsive to medical treatment with mean age 47 years Inclusion criteria: presence of HMB, reproductive age 35 to 50 years, completed family, failed appropriate first line oral medical therapy, normal PAP smear, no pelvic pathology at ultrasound, normal endometrial biopsy, PBAC >/= 100 (average of 2 consecutive cycles) Exclusion criteria: previous endometrial resection/ablation, previous insertion of LNG IUS, any uterine pathology on scan or hysteroscopy, any pathology where hysterectomy was indicated, not fully investigated abnormal uterine bleeding, postmenopausal bleeding
Interventions	1. LNG IUS inserted within 7 days of onset of menstruation under paracervical block 2. Laparoscopic supracervical hysterectomy (both performed by the same surgeons using the same technique)
Outcomes	Primary: • PBAC score at 12 months Secondary: • Quality of life (SF36)

	• Improvement in bleeding patterns • Intensity of postoperative pain (VAS scale 0 to 100 in categories) • Early postoperative complications requiring readmission Follow-up at 3, 6, 12 and 24 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated list"
Allocation concealment (selection bias)	Low risk	"serially numbered opaque sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of patients until interventions were assigned, surgeons performing the procedures blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Assessors blinded, but some outcomes based on patient self-report
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up or exclusions
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Groups appeared balanced at baseline and no other potential bias

Shabaan 2011

Methods	Single centre parallel group RCT No of women randomised: 112 No of women analysed: 95 (completed 12 months follow-up) Power calculation for sample size - 90% power, 15% attrition required 112 participants Authors claimed ITT analysis but no methods used to account for missing data Funding: Bayer Schering Pharma (LNG IUS), Proctor and Gamble (sanitary pads) and Assiut University (laboratory work)
Participants	Country: Egypt Women recruited from gynaecology outpatient clinics of Assiut University Hospital, with mean age 39 years Inclusion criteria: self described HMB, requested contraception, 20 to 50 years old at initial assessment, regular cycle, living close to hospital for follow-up

	Exclusion criteria: pregnancy, history of ectopic pregnancy, puerperal sepsis, pelvic inflammatory disease, evidence of defective coagulation, history or evidence of malignancy or hyperplasia in the endometrial biopsy, incidental adnexal abnormality on ultrasound, contraindications to COC, previous endometrial ablation/resection, uninvestigated postcoital bleeding, untreated abnormal cervical cytology, fibroids of any size
Interventions	1. LNG IUS 2. Low dose combined oral contraceptive pills (COC) - 30 mcg ethinyl estradiol and 150 mcg levonorgestrel. Follow-up at 6 and 12 months.
Outcomes	Primary: • Reduction of HMB at 12 months (alkaline haematin and PBAC) Secondary: • Treatment failure • Hb and ferritin levels • Quality of life (HRQoL questionnaire) Follow-up at 6 and 12 months
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated table of random numbers"
Allocation concealment (selection bias)	Low risk	Not explicitly stated but likely to be sealed envelopes opened with each new enrolment (similar to sister study by Sayed)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Substantial loss to follow-up and bleeding outcomes measured in only 64/112 at 12 months (because of treatment failure)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Groups appear comparable at baseline and no other potential bias

Shaw 2007

Methods	Single centre, parallel group RCT No of women randomised: 66 No of women analysed: 50 (completers at 12 months) - fewer women analysed because treatment failures not counted Power calculation for sample size: 30 women per group to have 80% power to detect a 50-point difference in PBAC scores between treatments Analysis was not by ITT (no method to account for missing data) Funding: ATOS Medical provided balloons and partly funded research nurse sessions
Participants	Country: UK Women with idiopathic menorrhagia in whom prior medical oral treatment had failed: mean age 42 or 43 years Inclusion criteria: aged 25 to 49 years, family complete, failed on appropriate first line oral medical therapy, normal histology on Pipelle endometrial biopsy, no pathology on pelvic ultrasound, normal cervical smear, PBAC score >120 (mean of two control cycles) Exclusion criteria: previous LNG IUS, previous endometrial resection/ablation, abnormal uterine bleeding not fully investigated, other pathology where hysterectomy was indicated, submucous fibroid identified on scan or hysteroscopy, uterine cavity < 7 cm or > 11 cm
Interventions	1. LNG IUS (Mirena) inserted in the uterine cavity just following menstruation 2. Thermal balloon ablation (Menotreat) - undertaken under general anaesthesia post menstruation without routine pretreatment
Outcomes	Primary: • PBAC scores at 12 months Secondary: • PBAC scores at 3, 6 and 9 months • Changes in Hb and ferritin concentrations between baseline and 6 months • Patient satisfaction • Continuance of the method at 2 years • Hysterectomy rates at 2 years • Teatment failure (additional medical treatment required, expulsion or removal of LNG IUS or total abdominal hysterectomy) Followup 3, 6, 9, 12 and 24 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer generated balanced random number blocks"
Allocation concealment (selection bias)	Low risk	"sequentially sealed opaque envelope" opened only when patient had signed the consent form

Shaw 2007 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Substantial attrition from trial by 12 months
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Groups appeared balanced at baseline and no other potential bias

Soysal 2002

Methods	Single centre study with parallel groups. No of women randomised: 72 No of women analysed: 66 (for primary outcome) No women lost to follow-up. Different denominators for other outcomes Power calculation for sample size - 30 patients per group to have 80% chance of detecting a mean difference of 15 mL in bleeding No ITT analysis (authors did not have a plan to deal with missing data). Source of funding not stated.
Participants	Country: Turkey Patients with mean age 44 years recruited from university medical centre. Inclusion criteria: age > 40 years; no further desire for childbearing; complaint of menorrhagia (defined by a PBAC score >150 for 2 months prior to the study); refused or non response to medical treatment Exclusion criteria: congenital and acquired uterine abnormalities; PID, breast cancer; pre malignant or malignant uterine disease; concomitant uterine disorders except iron deficiency anaemia; uterine volume > 8 weeks pregnancy or > 190 mL; pathologies (intramural or subserous fibroids > 2 cm); abnormalities on hysteroscopy
Interventions	1. LNG IUS inserted in the uterine cavity within first seven days of menstruation 2. Thermal balloon ablation with 2 months of pre-treatment with GnRH analogues to thin the endometrium) Follow-up at 3, 6 and 12 months.
Outcomes	Primary: • Reduction in menstrual bleeding; increase in Hb. Secondary: • Quality of life (SF36, HADS; • Side effects (including pain) • Patient satisfaction.

Soysal 2002 (*Continued*)

Notes	Study powered on menstrual blood loss, not quality of life. A much larger study would be required to adequately assess quality of life	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated randomisation"
Allocation concealment (selection bias)	Low risk	"numbered opaque sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal dropouts
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Groups appeared similar at baseline

TALIS 2006

Methods	Single centre, parallel groups No of women randomised: 83 (2 excluded post randomisation in each group leaving a total of 79) No of women analysed (for bleeding scores): 30 and 26 in LNG IUS group at 12 and 24 months, 29 and 20 in TBA group at 12 and 24 months (excluding failures) Lost to follow-up: 1 (12 months) and 3 (24 months) in LNG IUS group; 2 (12 months) and 8 (24 months) in TBA group. Power calculation for sample size based on 50-point PBAC difference - 30 women per group No ITT analysis. Funding was provided for sanitary pads and tampons but name of company was not reported
Participants	Country: NZ Patients with a complaint of heavy menstrual bleeding (mean age 41-43 years) recruited from hospital out patient clinic Inclusion criteria: completed family; age 25 to 50 years; regular cycle of menstruation, self described HMB Exclusion criteria: fibroids or polyps; FSH > 40; endometrial pathology; previous en-

TALIS 2006 (*Continued*)

	dometrial surgery; bleeding; suggested endometriosis
Interventions	1. LNG IUS (Mirena) 2. Balloon ablation (Thermachoice I)
Outcomes	Primary: • PBAC score • Quality of life (SF36) • Satisfaction rates at 3, 6, 12 and 24 months Secondary: • 'Failure' rates (expulsion/removal of LNG IUS or alternative therapy, initiation of medication or alternative surgery for TBA) • Amenorrhoea • Duration of bleeding • Adverse effects • Costs
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated randomisation" in blocks
Allocation concealment (selection bias)	Low risk	"consecutively numbered opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Minimal exclusions after randomisation (n = 4). These women were excluded because they did not fulfil inclusion criteria. Loss to follow-up was mostly minimal but > 20% were lost by 24 months in the TBA group
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Groups appeared similar at baseline

Tam 2006

Methods	Single centre, parallel group RCT No of women randomised: 44 No of women analysed: 33 (11 patients withdrew prior to receiving treatment) No power calculation for sample size No ITT analysis Funding: not stated
Participants	Country: Hong Kong Women with excessive menstrual bleeding recruited from outpatient gynaecology clinic, with mean age 44 and 45 years Inclusion criteria: premenopausal women > 40 years with a documented history of heavy menstruation for at least 3 months, completed family or no desire for future fertility, HMB had failed to respond to conventional medical therapy, not currently on hormonal treatment Exclusion criteria: uterus >10 weeks gravid uterine size, presence of submucosal fibroids or endometrial polyps, any contraindications for progestogen use or an intrauterine device, evidence of cervical or endometrial malignancy
Interventions	1. LNG IUS inserted following diagnostic hysteroscopy 2. Thermal balloon endometrial ablation (Thermachoice) performed 6 weeks after thinning with GnRH analogue or oral danazol
Outcomes	• Menstrual bleeding (amenorrhoea, hypomenorrhoea and normal rates of bleeding) • Side effects • HB and iron status • Health status function (SF36)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer generated random number series"
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque sealed envelopes (personal correspondence with author)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded

Tam 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Substantial exclusions post randomisation and prior to treatment - greater in TBA group
Selective reporting (reporting bias)	Unclear risk	Authors stated that side effects of treatment were assessed but these were not reported clearly
Other bias	Low risk	Groups appear comparable at baseline and no other potential bias

COC: combined oral contraceptive
DVT: deep vein thrombosis
EQ-5D: Euroqol Group 5-Dimension Self Report Questionnaire
Fe: iron
FSH: follicle stimulating hormone
GnRH: gonadotropin-releasing hormone
HADS: Hospital Anxiety and Depression Scale
Hb: haemoglobin
HMB: heavy menstrual bleeding
HT: hormone therapy
ITT: intention-to-treat
IUCD: intrauterine contraceptive device
LNG IUS: levonorgestrel-releasing intrauterine system
MPA: medroxyprogesterone acetate
MRI: magnetic resonance imaging
NET: norethisterone acetate
NSAID: non-steroidal anti-inflammatory drug
OC: oral contraceptive
PBAC: pictorial blood loss assessment chart
PID: Pelvic inflammatory disease
RCT: randomised controlled trial
SD: standard deviation
SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey
TBA: thermal balloon ablation
TCRE: transcervical resection of the endometrium
TMFL: total menstrual fluid loss
TVUS: transvaginal ultrasound
VAS: visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abu Hashim 2013	Participants had pathology - endometrial hyperplasia
Endrikat 2009	Participants were randomised in order of arrival at the treatment centre - quasi randomisation, which is an exclusion criterion
Ghazizadeh 2011	Although the study was described as random, the authors stated that participants were allowed to choose their treatment
Gupta 2006	Relevant comparison but participants were able to choose their treatment and were not randomised
Janssen 1999	This randomised double-blind trial compared the effects of a multiload intrauterine device releasing 0.0 (control group), 1.5, 3.0 and 6.0 ug of 3-ketodesogestrel daily on menstrual blood loss but 22% of the participants did not have heavy menstrual bleeding
Karacaoglu 2001	This study was written in Turkish and translated by Metin G. There is no indication that it was randomised
Karimi-Zarchi 2013	Participants had pathology - endometrial hyperplasia
Kucuk 2008	Quasi-randomised trial - "by a predefined application order"
Lahteenmaki 1998	This study did not measure any of the review's outcomes
Lee 2013	Observational cohort study - participants were not randomised
Milsom 1991	This study compared flurbiprofen (an NSAID), tranexamic acid and LNG IUS in 35 women with menorrhagia. The first 20 consecutive women were treated with LNG IUS and the remaining 15 women were randomised to either flurbiprofen or tranexamic acid in a cross-over design. The reduction in menstrual blood loss was compared between all treatments. The LNG IUS arm was not randomised, so the study has been excluded
Rogerson 1999	This trial experienced difficulties in recruiting patients and was stopped
Romer 2000	This study was a controlled comparative study with equal numbers of patients in each group, endometrial ablation and LNG IUS. There is no indication that it was randomised
Tosun 2014	Substantially biased study with large imbalance in dropouts - so final results not informative

LNG IUS: levonorgestrel-releasing intrauterine system
NSAID: non-steroidal anti-inflammatory

Characteristics of studies awaiting assessment *[ordered by study ID]*

Ghazizadeh 2014

Methods	RCT, open label but different numbers in each randomised group
Participants	Women aged 35 to 45 years of age, candidates for hysterectomy, previously treated with hormonal therapy for at least 6 months without therapeutic response
Interventions	Comparisons between Novasure, LNG IUS and hysteroscopic endometrial resection. Follow- up 6 to 12 months
Outcomes	Menstrual blood loss, complications and satisfaction
Notes	Findings to be added at next update

McMillan 1998

Methods	unknown
Participants	
Interventions	
Outcomes	
Notes	

McMillan 2005

Methods	unknown
Participants	
Interventions	
Outcomes	
Notes	

LNG IUS: levonorgestrel-releasing intrauterine system
RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Abdel-Alim 2003

Trial name or title	Evaluation of the role of LNG IUS in management of menorrhagia
Methods	
Participants	Women with dysfunctional uterine bleeding attending clinics at Assiut University Hospital, Egypt
Interventions	(1) LNG IUS (Mirena) (2) Low dose combined oral contraceptive pills
Outcomes	Primary: - Menstrual blood loss measured at 1, 3 and 6 months follow-up by PBAC and patient subjective assessment of blood loss - Health-related quality of life assessment Secondary: - No of days bleeding - Doppler assessment of blood flow in uterine and myometrial vessels - Patient compliance - Patient acceptability - Adverse events - Resource use/cost
Starting date	Not known
Contact information	Dr Sherif Abdelrazik Assistant Lecturer of Obstetrics and Gynaecology Assuit University Egypt Email: abdelrazik@yahoo.com
Notes	Part one of a trial being submitted in partial fulfilment of MD degree in Obstetrics and Gynaecology

Herman 2013

Trial name or title	Herman 2013, Identifier (Dutch trial register) NTR2984
Methods	Multicentre parallel group RCT organised in network infrastructure in Netherlands where general practitioners and gynaecologists collaborate
Participants	Women >/= 34 years with heavy menstrual bleeding, PBAC score >150 points and no future wish for childbearing
Interventions	LNG IUS versus endometrial ablation (Novasure)
Outcomes	Primary: PBAC score at 24 months follow- up Secondary: Patient satisfaction, complications, number of reinterventions, menstrual bleeding pattern, quality of life, sexual function, sick leave and costs

Herman 2013 (*Continued*)

Starting date	Not reported
Contact information	M. Herman (Principal author) m.herman@mmc.nl
Notes	

SHiPP 2013

Trial name or title	SHiPP (Stopping Heavy Periods Project), Identifier NCT02002260
Methods	Parallel group RCT, open label. Randomisation by permuted blocks with a variable block size
Participants	Women presenting for gynaecologic care with a self report of heavy menstrual bleeding secondary to ovulatory disorders or endometrial haemostatic disorders. Age 18 to 51 years. Plan to recruit 212 women
Interventions	LNG IUS compared with combined oral contraceptives (any combined oral contraceptive chosen by primary care provider provided it contains 30 to 35 mg of ethinyl estradiol)
Outcomes	Primary: Menstrual bleeding questionnaire (quality of life) at randomisation, 6 weeks, 3, 6 and 12 months Secondary: Treatment failure
Starting date	February 2013 - estimated completion date January 2017
Contact information	Kristen Matteson Assistant Professor of Obstetrics and Gynecology Women and Infants Hospital of Rhode Island USA
Notes	Conducted in primary care centres

LNG IUS: levonorgestrel-releasing intrauterine system
PBAC: pictorial blood loss assessment chart
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. IUS versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean PBAC score at 6 months follow-up	1	40	Mean Difference (IV, Fixed, 95% CI)	-99.5 [-115.75, -83.25]

Comparison 2. IUS versus any other medical treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean menstrual blood loss at end of study	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Alkaline haematin method (mL)	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 PBAC score	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Percentage reduction in blood loss at end of study (from baseline)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Alkaline haematin method	2	170	Mean Difference (IV, Random, 95% CI)	66.91 [42.61, 91.20]
2.2 PBAC score	3	335	Mean Difference (IV, Random, 95% CI)	55.05 [27.83, 82.28]
3 Menstrual blood loss by alkaline haematin - descriptive results			Other data	No numeric data
4 PBAC scores for menstrual blood loss - descriptive results			Other data	No numeric data
5 Amenorrhoea (greater than three months)	1	35	Risk Ratio (M-H, Fixed, 95% CI)	11.05 [0.67, 182.23]
6 Total menstrual fluid loss - descriptive results			Other data	No numeric data
7 Proportion of women satisfied with treatment	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.78, 2.62]
8 Quality of life (good or excellent)	2	170	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.72, 2.00]
9 Quality of life (unhealthy days and lost days)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Unhealthy days in past month (physical)	2	170	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-2.17, -0.63]
9.2 Unhealthy days in past month (mental)	2	170	Mean Difference (IV, Fixed, 95% CI)	1.44 [0.61, 2.27]
9.3 Activity limitation in past month (lost days)	2	170	Mean Difference (IV, Fixed, 95% CI)	-5.07 [-5.79, -4.35]
10 Quality of life scores (between group difference in SF36 over 2 years)	1		Mean Difference (Fixed, 95% CI)	Subtotals only

10.1 Overall MMAS	1		Mean Difference (Fixed, 95% CI)	13.40 [9.89, 16.91]
10.2 SF36: physical functioning	1		Mean Difference (Fixed, 95% CI)	2.7 [-0.00, 5.40]
10.3 SF36: physical role	1		Mean Difference (Fixed, 95% CI)	5.90 [2.65, 9.15]
10.4 Emotional role	1		Mean Difference (Fixed, 95% CI)	4.6 [1.25, 7.95]
10.5 Social functioning	1		Mean Difference (Fixed, 95% CI)	5.10 [2.04, 8.16]
10.6 Mental health	1		Mean Difference (Fixed, 95% CI)	1.5 [-0.95, 3.95]
10.7 Energy and vitality	1		Mean Difference (Fixed, 95% CI)	5.3 [2.46, 8.14]
10.8 Pain	1		Mean Difference (Fixed, 95% CI)	7.8 [4.55, 11.05]
10.9 Perception of general health	1		Mean Difference (Fixed, 95% CI)	2.9 [0.06, 5.74]
10.10 EQ5D descriptive	1		Mean Difference (Fixed, 95% CI)	0.01 [-0.02, 0.04]
10.11 EQ5D visual analogue scale	1		Mean Difference (Fixed, 95% CI)	2.0 [-0.55, 4.55]
11 Proportion of women with serious side effects	1	571	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.61, 1.28]
12 Individual adverse effects	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Pelvic pain	3	784	Risk Ratio (M-H, Fixed, 95% CI)	2.68 [1.00, 7.18]
12.2 Mood swings	1	31	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.60, 1.95]
12.3 Intermenstrual bleeding and menstrual irregularity	1	31	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [0.83, 12.00]
12.4 Breast tenderness	3	244	Risk Ratio (M-H, Fixed, 95% CI)	2.85 [1.29, 6.29]
12.5 Nausea	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.10, 2.59]
12.6 Diarrhoea	1	51	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.03, 2.17]
12.7 Upper respiratory infection	2	213	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [0.67, 4.44]
12.8 Ovarian cysts	3	784	Risk Ratio (M-H, Fixed, 95% CI)	3.28 [1.31, 8.21]
12.9 Headache	3	784	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.68, 1.88]
12.10 Vaginitis	1	162	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [0.86, 10.95]
12.11 Acne	1	162	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.31, 3.41]
12.12 Hypertension	1	162	Risk Ratio (M-H, Fixed, 95% CI)	5.13 [0.61, 42.90]
12.13 Sinusitis	1	162	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [0.42, 6.91]
12.14 Fatigue	1	162	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.39, 10.88]
12.15 Urinary tract infection	1	162	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.53, 7.92]
12.16 Increased weight	1	162	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.23, 2.94]
12.17 Lower abdominal pain	1	162	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.15, 2.49]
13 Withdrawal from treatment because of adverse events	3	780	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.80, 1.69]
14 Withdrawal of treatment for any reason	1	571	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.49, 0.70]
15 Failure of treatment	3	327	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.18, 0.40]

Comparison 3. IUS versus endometrial ablation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PBAC score at 12 months	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Improvement in HMB within 12 months (amenorrhoea, hypomenorrhoea or eumenorrhoea)	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Amenorrhoea	8	431	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.85, 1.72]
2.2 Hypomenorrhoea	4	200	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.73, 1.33]
2.3 Eumenorrhoea	3	160	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.30, 1.00]
2.4 Improvement in bleeding pattern	3	172	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.02, 1.41]
3 PBAC score after treatment (descriptive results)			Other data	No numeric data
4 Proportion of women satisfied with treatment	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Within one year follow-up	5	317	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.85, 1.07]
4.2 After 1 year and up to 5 years follow-up	2	102	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.95, 1.31]
5 Quality of life (SF36) within 12 months follow-up	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Physical functioning	1	33	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-11.10, 4.90]
5.2 Role limitation (physical)	1	33	Mean Difference (IV, Fixed, 95% CI)	-2.5 [-9.32, 4.32]
5.3 Bodily pain	1	33	Mean Difference (IV, Fixed, 95% CI)	0.40 [-6.43, 7.23]
5.4 General health	1	33	Mean Difference (IV, Fixed, 95% CI)	-14.40 [-22.63, -6.17]
5.5 Vitality	1	33	Mean Difference (IV, Fixed, 95% CI)	-5.20 [-11.46, 1.06]
5.6 Social functioning	1	33	Mean Difference (IV, Fixed, 95% CI)	-6.70 [-12.82, -0.58]
5.7 Role limitation (emotional)	1	33	Mean Difference (IV, Fixed, 95% CI)	-10.10 [-17.03, -3.17]
5.8 Mental health	1	33	Mean Difference (IV, Fixed, 95% CI)	-11.20 [-17.08, -5.32]
5.9 Overall SF36 score	1	79	Mean Difference (IV, Fixed, 95% CI)	2.60 [-5.98, 11.18]
6 Quality of life (QOL) scores at 12 months (SF36) - descriptive results			Other data	No numeric data
7 Quality of life within 5 years follow-up (proportion with improved wellbeing)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Physical	1	52	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.11, 1.92]
7.2 Emotional	1	52	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.09, 2.30]
8 Quality of life within 5 years - psychological wellbeing (continuous)	1	28	Mean Difference (IV, Fixed, 95% CI)	10.30 [-6.18, 26.78]
9 Total proportion of women with side effects	3	201	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [1.44, 2.94]
10 Individual side effects	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Endometritis	2	120	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.21, 2.35]

10.2 Pelvic pain or PID	3	180	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.46, 3.01]
10.3 Myometritis	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.02, 8.89]
10.4 Adenomyosis	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.02, 8.89]
10.5 Abnormal PAP	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 2.99]
10.6 Oedema	1	41	Risk Ratio (M-H, Fixed, 95% CI)	3.45 [0.15, 80.03]
10.7 Breast pain	3	201	Risk Ratio (M-H, Fixed, 95% CI)	7.57 [1.78, 32.23]
10.8 Weight gain	2	141	Risk Ratio (M-H, Fixed, 95% CI)	2.60 [1.16, 5.84]
10.9 Mood swings	2	132	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.36, 15.32]
10.10 Bloating	2	141	Risk Ratio (M-H, Fixed, 95% CI)	4.57 [1.63, 12.82]
10.11 Acne or greasy skin	3	201	Risk Ratio (M-H, Fixed, 95% CI)	8.40 [1.57, 44.76]
10.12 Nausea	1	72	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.50, 161.29]
10.13 Headache	3	201	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.64, 6.50]
10.14 Leg pain	2	141	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.32, 28.57]
10.15 Dysmenorrhoea	2	151	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.17]
10.16 Lower abdominal pain	4	242	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.55, 4.97]
10.17 Actinomycoses	1	79	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.12, 69.74]
10.18 Decreased libido	1	69	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.15, 6.90]
10.19 Hair loss	1	69	Risk Ratio (M-H, Fixed, 95% CI)	5.14 [0.26, 103.35]
10.20 Anxiety or depression	1	69	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [0.20, 21.67]
10.21 Hypertension	1	69	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [0.13, 73.21]
10.22 Endometriosis	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.02, 8.89]
10.23 Bleeding or spotting	4	241	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.74, 2.58]
10.24 Hematometra	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.87]
10.25 Vaginitis	1	60	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.40, 10.11]
10.26 Genital ulceration	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.87]
11 Treatment failure	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Up to 12 months follow-up	6	390	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.99, 2.52]
11.2 More than 12 months follow-up	4	259	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.72, 1.71]
12 Total cost per woman			Other data	No numeric data

Comparison 4. IUS versus hysterectomy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PBAC score (at 12 months follow-up)			Other data	No numeric data
1.1 At 12 months follow-up			Other data	No numeric data
1.2 At 24 months follow-up			Other data	No numeric data
2 Satisfaction with treatment (5 years follow-up)	1	232	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.94, 1.08]
3 Quality of life scores at 12 months follow-up (descriptive data)			Other data	No numeric data
4 Quality of life scores at end of study (final values)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 SF36: General health	1	72	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-6.03, 4.43]

4.2 SF36: Physical function	1	72	Mean Difference (IV, Fixed, 95% CI)	-5.00 [-10.77, 0.77]
4.3 SF36: Role (physical)	1	72	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-7.21, 3.21]
4.4 SF36: Role (emotional)	1	72	Mean Difference (IV, Fixed, 95% CI)	16.10 [8.88, 23.32]
4.5 SF36: Mental health	1	72	Mean Difference (IV, Fixed, 95% CI)	36.8 [30.37, 43.23]
4.6 SF36: Social function	1	72	Mean Difference (IV, Fixed, 95% CI)	1.80 [-5.00, 8.60]
4.7 SF36: Vitality	1	72	Mean Difference (IV, Fixed, 95% CI)	5.60 [-0.78, 11.98]
4.8 SF36: Pain	1	72	Mean Difference (IV, Fixed, 95% CI)	-14.80 [-23.31, -6.29]
5 Quality of life scores at end of study (change values)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 EQ-5D	1	221	Mean Difference (IV, Fixed, 95% CI)	-1.09 [-1.15, -1.03]
5.2 SF36: General health	1	221	Mean Difference (IV, Fixed, 95% CI)	2.2 [-2.93, 7.33]
5.3 SF36: Physical functioning	1	221	Mean Difference (IV, Fixed, 95% CI)	0.40 [-5.51, 6.31]
5.4 SF36: Emotional wellbeing	1	221	Mean Difference (IV, Fixed, 95% CI)	2.5 [-3.35, 8.35]
5.5 SF36: Social functioning	1	221	Mean Difference (IV, Fixed, 95% CI)	6.10 [-1.47, 13.67]
5.6 SF36: Energy/vitality	1	221	Mean Difference (IV, Fixed, 95% CI)	0.70 [-5.67, 7.07]
5.7 SF36: Pain	1	221	Mean Difference (IV, Fixed, 95% CI)	0.40 [-7.32, 8.12]
5.8 SF36: Role - physical	1	221	Mean Difference (IV, Fixed, 95% CI)	5.00 [-7.49, 17.49]
5.9 SF36: Role - emotional	1	221	Mean Difference (IV, Fixed, 95% CI)	4.20 [-10.03, 18.43]
5.10 General Health - VAS	1	221	Mean Difference (IV, Fixed, 95% CI)	3.00 [-2.74, 8.74]
6 Early adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Headache	1	86	Risk Ratio (M-H, Fixed, 95% CI)	11.0 [0.63, 192.99]
6.2 Breast tenderness	1	86	Risk Ratio (M-H, Fixed, 95% CI)	7.0 [0.37, 131.56]
6.3 Acne	1	86	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.25, 101.18]
6.4 Depressive episode	2	318	Risk Ratio (M-H, Fixed, 95% CI)	3.96 [0.45, 35.06]
6.5 Wound infection	2	307	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.05, 0.66]
6.6 Infected pelvic haematoma	1	232	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.54, 4.01]
6.7 Postoperative fever	1	232	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.05, 5.35]
6.8 Urinary retention	1	232	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.17]
6.9 Bladder perforation	1	232	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.69]
6.10 Bowel perforation	1	232	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.96]
6.11 Wound rupture	1	232	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.05]
6.12 Peritonitis	1	232	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.96]
6.13 Ileus	1	232	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.05]
6.14 Severe abdominal pain	1	232	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [0.50, 7.67]
6.15 Vesicovaginal fistula	1	232	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.96]
6.16 Postoperative bleeding	1	232	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.05, 5.35]
6.17 Intestinal occlusion	1	232	Risk Ratio (M-H, Fixed, 95% CI)	2.95 [0.12, 71.65]
6.18 Ureter lesion	1	232	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.96]
6.19 Thromboembolic disease	1	232	Risk Ratio (M-H, Fixed, 95% CI)	2.95 [0.12, 71.65]
7 Later adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Back pain (increase from baseline)	1	232	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.42, 0.80]
7.2 Abdominal pain (increase from baseline)	1	232	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.30, 1.22]
7.3 Urge incontinence	1	221	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.39, 1.35]
7.4 Stress incontinence	1	221	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.48, 1.01]
7.5 Urinary tract infections	1	221	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.20, 1.03]
7.6 Incidence of ovarian cysts	1	180	Risk Ratio (M-H, Fixed, 95% CI)	2.72 [1.24, 5.97]
8 Total cost per woman			Other data	No numeric data
8.1 At 12 months follow-up			Other data	No numeric data

8.2 At 5 years follow-up	Other data	No numeric data
8.3 At 10 years follow-up	Other data	No numeric data

Analysis 1.1. Comparison 1 IUS versus placebo or no treatment, Outcome 1 Mean PBAC score at 6 months follow-up.

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 1 IUS versus placebo or no treatment

Outcome: 1 Mean PBAC score at 6 months follow-up

Study or subgroup	IUS N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kilic 2009	20	155.6 (24.05)	20	255.1 (28.22)		100.0 %	-99.50 [-115.75, -83.25]
Total (95% CI)	**20**		**20**			**100.0 %**	**-99.50 [-115.75, -83.25]**

Heterogeneity: not applicable

Test for overall effect: Z = 12.00 (P < 0.00001)

Test for subgroup differences: Not applicable

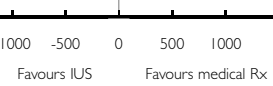
Analysis 2.1. Comparison 2 IUS versus any other medical treatment, Outcome 1 Mean menstrual blood loss at end of study.

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 2 IUS versus any other medical treatment

Outcome: 1 Mean menstrual blood loss at end of study

Study or subgroup	Favours IUS N	Mean(SD)	Medical Rx N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Alkaline haematin method (mL)						
Sayed 2011	29	19.4 (36.5)	29	193 (36.2)		-173.60 [-192.31, -154.89]
Shabaan 2011	56	44.4 (34.9)	56	118.2 (75)		-73.80 [-95.47, -52.13]
2 PBAC score						
Sayed 2011	29	33.7 (43.5)	29	153.9 (156.1)		-120.20 [-179.18, -61.22]
Shabaan 2011	56	31.6 (35.1)	56	273 (238.4)		-241.40 [-304.51, -178.29]



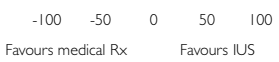
Analysis 2.2. Comparison 2 IUS versus any other medical treatment, Outcome 2 Percentage reduction in blood loss at end of study (from baseline).

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 2 IUS versus any other medical treatment

Outcome: 2 Percentage reduction in blood loss at end of study (from baseline)

Study or subgroup	IUS N	Mean(SD)	Medical Rx N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Alkaline haematin method							
Shabaan 2011	56	87.4 (11.3)	56	35 (77)		42.2 %	52.40 [32.02, 72.78]
Sayed 2011	29	90.9 (12.8)	29	13.4 (11.1)		57.8 %	77.50 [71.33, 83.67]
Subtotal (95% CI)	**85**		**85**			**100.0 %**	**66.91 [42.61, 91.20]**
Heterogeneity: Tau^2 = 255.98; Chi^2 = 5.34, df = 1 (P = 0.02); I^2 =81%							
Test for overall effect: Z = 5.40 (P < 0.00001)							
2 PBAC score							
Sayed 2011	29	88 (16.5)	29	53.5 (51.2)		34.7 %	34.50 [14.92, 54.08]
Kaunitz 2010	82	70.8 (88.3)	83	21.5 (35.8)		34.0 %	49.30 [28.69, 69.91]
Shabaan 2011	56	86.6 (17)	56	2.5 (93.2)		31.3 %	84.10 [59.29, 108.91]
Subtotal (95% CI)	**167**		**168**			**100.0 %**	**55.05 [27.83, 82.28]**
Heterogeneity: Tau^2 = 456.56; Chi^2 = 9.56, df = 2 (P = 0.01); I^2 =79%							
Test for overall effect: Z = 3.96 (P = 0.000074)							



Analysis 2.3. Comparison 2 IUS versus any other medical treatment, Outcome 3 Menstrual blood loss by alkaline haematin - descriptive results.

Menstrual blood loss by alkaline haematin - descriptive results

Study	Prog IUS	Medical treatment	Follow-up	Statistical test	Notes
Cameron 1987	Median = 55 mL, range = 31 to 75 mL n = 8 Treatment groups were not comparable at baseline and there were no statistical tests comparing the after treatment values between	Norethisterone group: median = 106 mL range = 24 to 216, n = 8 Mefenamic acid group: median = 51 m: range = 45 to 203 mL, n=8 Danazol group: me-	2 months	No statistical tests were performed comparing values between groups	The treatment groups were not comparable at baseline

Menstrual blood loss by alkaline haematin - descriptive results (*Continued*)

	groups	dian = 54 mL range = 30 to 347 mL, n = 6			
Irvine 1998	Median = 6 mL, range = 0 to 284 mL n = 22	Norethisterone group: Median=20mls, range=4-137mls n=22	3 months	Wilcoxon rank-sum test: t = 315.5, P value = 0.033	
Kaunitz 2010	Absolute change from baseline: Median = -128.8 mL, range -393.6 to 1242.2 mL n = 80	Absolute change from baseline: Medroxyproges-terone group: Median = -17.8 mL, range -271.5 to 78.6 mL n = 82	6 months	Wilcoxon rank-sum test, P < 0.001	
Reid 2005	Median = 5 mL, range = 0 to 45 mL n = 25	Mefenamic acid group: Median = 100 mL, range = 46 to 168 mL n = 26	6 months	Wilcoxon rank-sum test: P value < 0.001 (for MBL at 6 months follow-up between groups, summary figures not supplied)	

Analysis 2.4. Comparison 2 IUS versus any other medical treatment, Outcome 4 PBAC scores for menstrual blood loss - descriptive results.

PBAC scores for menstrual blood loss - descriptive results

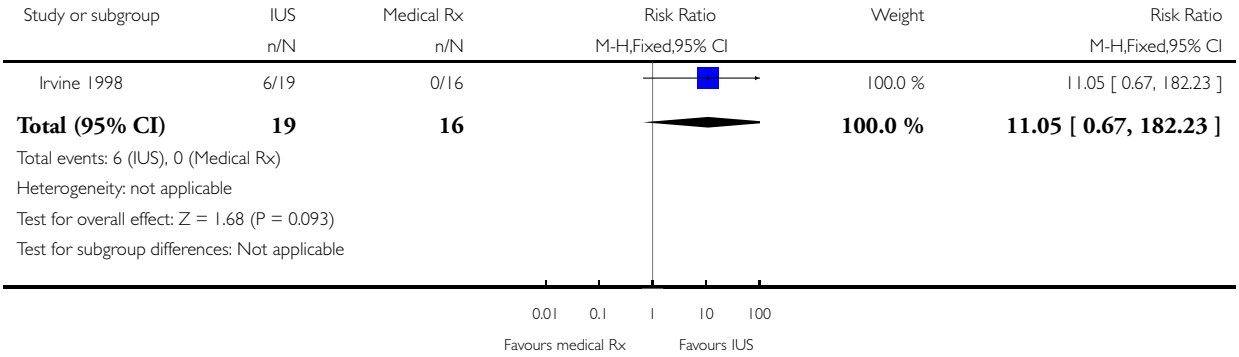
Study	**IUS group**	**Control group**	**Follow-up**	**Statistical test**	**Notes**
Reid 2005	Median = 25, range = 0 to 402 n = 25	Mefenamic acid group: Median = 159, range = 50 to 307 n = 26	Follow-up = 6 months	Wilcoxon rank-sum test: P value < 0.001 (for MBL at 6 months follow-up between groups, summary figures not supplied)	

Analysis 2.5. Comparison 2 IUS versus any other medical treatment, Outcome 5 Amenorrhoea (greater than three months).

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 2 IUS versus any other medical treatment

Outcome: 5 Amenorrhoea (greater than three months)



Analysis 2.6. Comparison 2 IUS versus any other medical treatment, Outcome 6 Total menstrual fluid loss - descriptive results.

Total menstrual fluid loss - descriptive results

Study	IUS group	Control group	Follow-up	Statistical test	Notes
Reid 2005	Median = 27, range = 0 to 156 n = 25	Median = 157, range = 76 to 319 n = 25	6 months	Wilcoxon rank-sum test: P value < 0.001 (for values at 6 months follow-up between groups, summary figures not supplied)	The authors claim that this is the first study to measure total fluid menstrual loss as opposed to menstrual blood loss

Analysis 2.7. Comparison 2 IUS versus any other medical treatment, Outcome 7 Proportion of women satisfied with treatment.

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 2 IUS versus any other medical treatment

Outcome: 7 Proportion of women satisfied with treatment

Study or subgroup	IUS n/N	Medical Rx n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Irvine 1998	14/22	8/18		100.0 %	1.43 [0.78, 2.62]
Total (95% CI)	**22**	**18**		**100.0 %**	**1.43 [0.78, 2.62]**
Total events: 14 (IUS), 8 (Medical Rx)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.16 (P = 0.25)					
Test for subgroup differences: Not applicable					

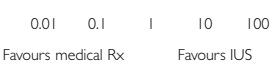
Analysis 2.8. Comparison 2 IUS versus any other medical treatment, Outcome 8 Quality of life (good or excellent).

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 2 IUS versus any other medical treatment

Outcome: 8 Quality of life (good or excellent)

Study or subgroup	IUS n/N	Medical Rx n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sayed 2011	9/29	7/29		35.0 %	1.29 [0.55, 2.99]
Shabaan 2011	15/56	13/56		65.0 %	1.15 [0.61, 2.20]
Total (95% CI)	**85**	**85**		**100.0 %**	**1.20 [0.72, 2.00]**
Total events: 24 (IUS), 20 (Medical Rx)					
Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 0.70 (P = 0.48)					
Test for subgroup differences: Not applicable					



Analysis 2.9. Comparison 2 IUS versus any other medical treatment, Outcome 9 Quality of life (unhealthy days and lost days).

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 2 IUS versus any other medical treatment

Outcome: 9 Quality of life (unhealthy days and lost days)

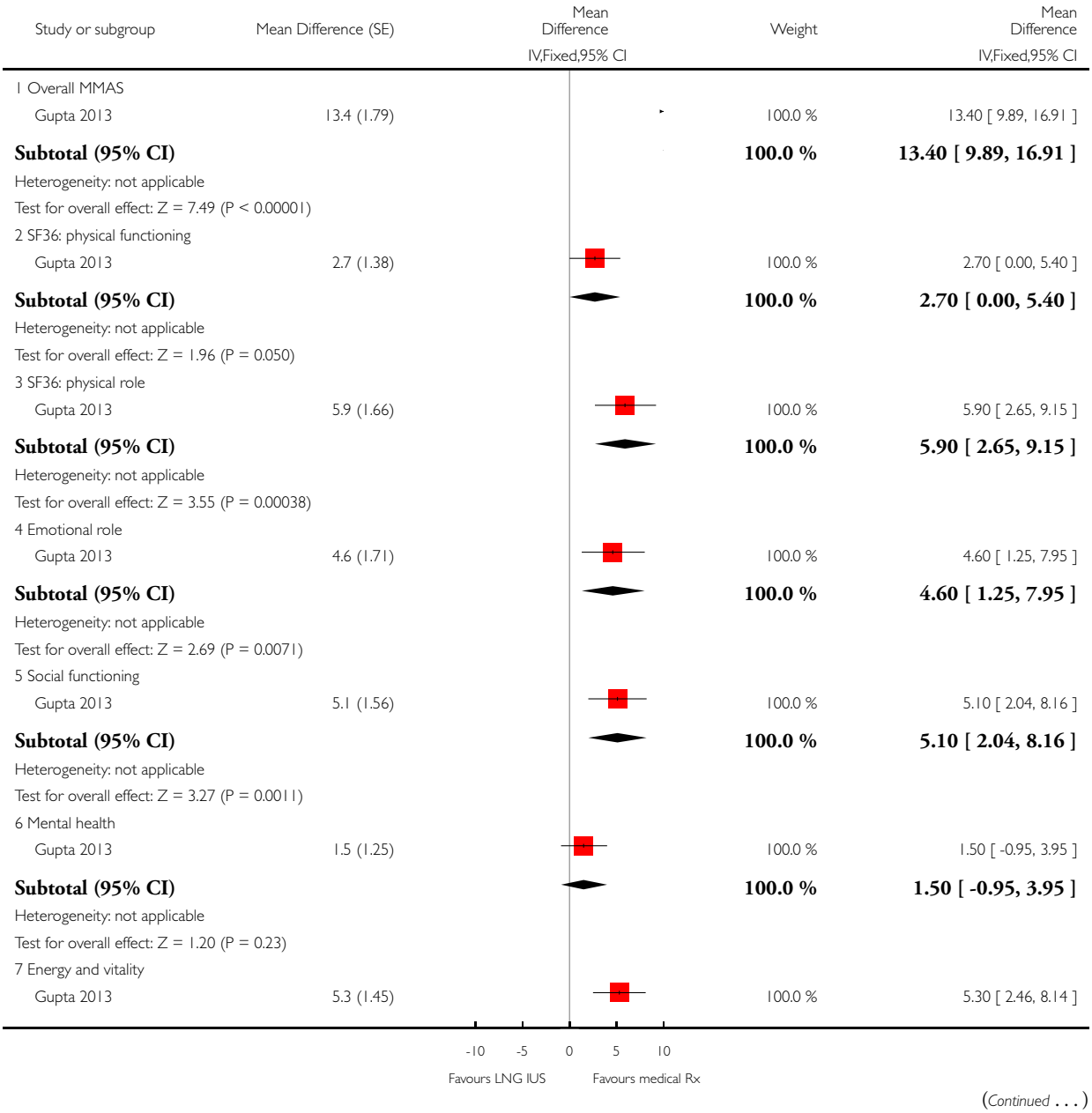
Study or subgroup	LNG IUS N	Mean(SD)	Medical Rx N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Unhealthy days in past month (physical)							
Sayed 2011	29	3.7 (3.2)	29	6.4 (3)		23.3 %	-2.70 [-4.30, -1.10]
Shabaan 2011	56	3.7 (2)	56	4.7 (2.7)		76.7 %	-1.00 [-1.88, -0.12]
Subtotal (95% CI)	**85**		**85**			**100.0 %**	**-1.40 [-2.17, -0.63]**
Heterogeneity: Chi^2 = 3.34, df = 1 (P = 0.07); I^2 =70%							
Test for overall effect: Z = 3.55 (P = 0.00038)							
2 Unhealthy days in past month (mental)							
Sayed 2011	29	6.6 (3.7)	29	8.7 (3.6)		19.5 %	-2.10 [-3.98, -0.22]
Shabaan 2011	56	6.7 (3.1)	56	4.4 (1.7)		80.5 %	2.30 [1.37, 3.23]
Subtotal (95% CI)	**85**		**85**			**100.0 %**	**1.44 [0.61, 2.27]**
Heterogeneity: Chi^2 = 16.95, df = 1 (P = 0.00004); I^2 =94%							
Test for overall effect: Z = 3.40 (P = 0.00068)							
3 Activity limitation in past month (lost days)							
Sayed 2011	29	1.3 (1.5)	29	6.3 (3.3)		29.5 %	-5.00 [-6.32, -3.68]
Shabaan 2011	56	1.6 (2.4)	56	6.7 (2.2)		70.5 %	-5.10 [-5.95, -4.25]
Subtotal (95% CI)	**85**		**85**			**100.0 %**	**-5.07 [-5.79, -4.35]**
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.90); I^2 =0.0%							
Test for overall effect: Z = 13.88 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 138.87, df = 2 (P = 0.00), I^2 =99%							

Analysis 2.10. Comparison 2 IUS versus any other medical treatment, Outcome 10 Quality of life scores (between group difference in SF36 over 2 years).

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 2 IUS versus any other medical treatment

Outcome: 10 Quality of life scores (between group difference in SF36 over 2 years)



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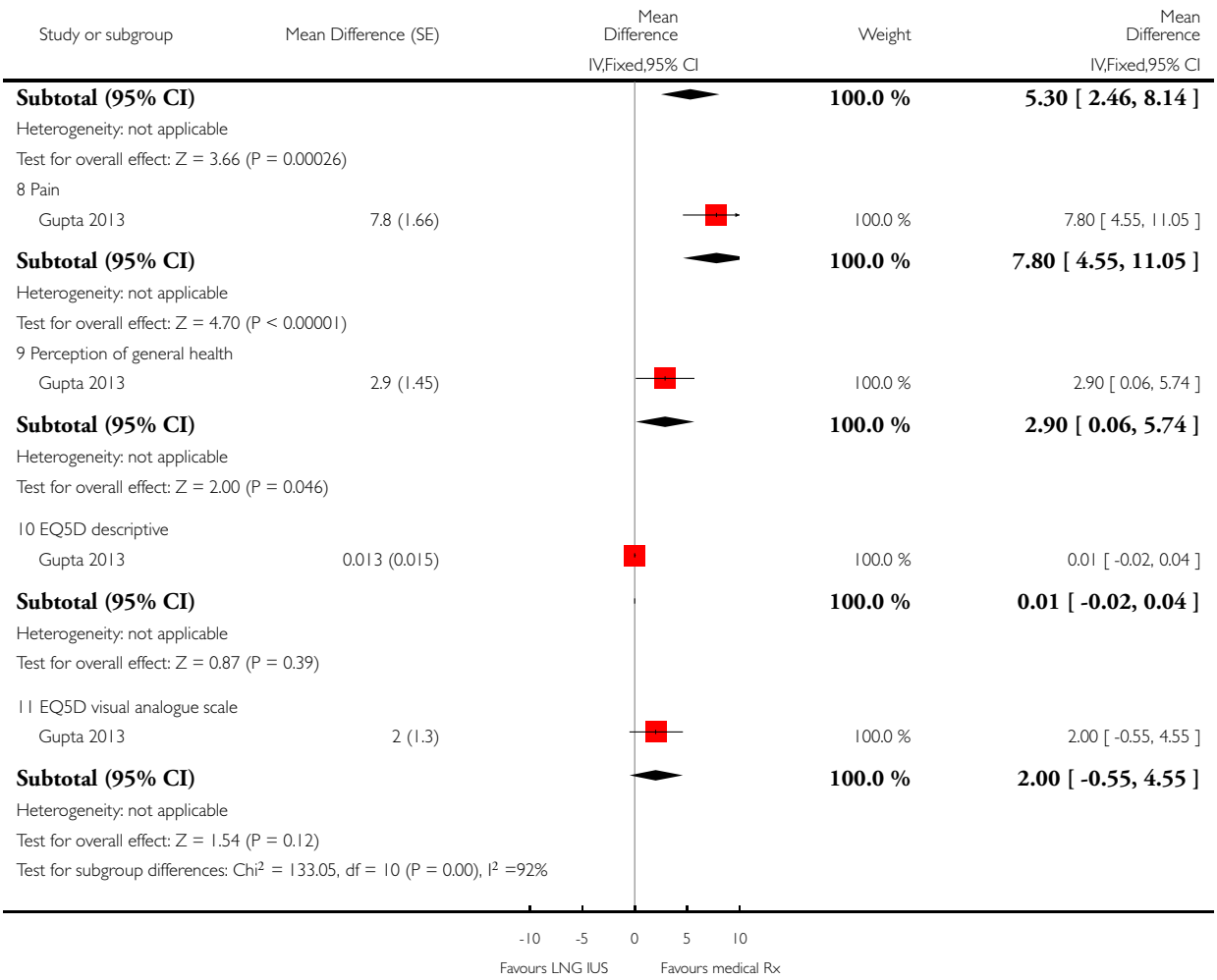

Analysis 2.11. Comparison 2 IUS versus any other medical treatment, Outcome 11 Proportion of women with serious side effects.

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 2 IUS versus any other medical treatment

Outcome: 11 Proportion of women with serious side effects

Study or subgroup	IUS n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gupta 2013	45/285	51/286		100.0 %	0.89 [0.61, 1.28]
Total (95% CI)	**285**	**286**		**100.0 %**	**0.89 [0.61, 1.28]**
Total events: 45 (IUS), 51 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.65 (P = 0.51)					
Test for subgroup differences: Not applicable					

Analysis 2.12. Comparison 2 IUS versus any other medical treatment, Outcome 12 Individual adverse effects.

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 2 IUS versus any other medical treatment

Outcome: 12 Individual adverse effects

Study or subgroup	IUS n/N	Medical Rx n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Pelvic pain					
Gupta 2013	1/285	1/286		20.2 %	1.00 [0.06, 15.97]
Kaunitz 2010	4/80	2/82		40.0 %	2.05 [0.39, 10.88]
Reid 2005	8/25	2/26		39.7 %	4.16 [0.98, 17.72]
Subtotal (95% CI)	**390**	**394**		**100.0 %**	**2.68 [1.00, 7.18]**
Total events: 13 (IUS), 5 (Medical Rx)					
Heterogeneity: Chi^2 = 0.94, df = 2 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 1.95 (P = 0.051)					
2 Mood swings					
Irvine 1998	12/19	7/12		100.0 %	1.08 [0.60, 1.95]

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Study or subgroup	IUS n/N	Medical Rx n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**19**	**12**		**100.0 %**	**1.08 [0.60, 1.95]**
Total events: 12 (IUS), 7 (Medical Rx)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.26 (P = 0.79)					
3 Intermenstrual bleeding and menstrual irregularity					
Irvine 1998	10/19	2/12		100.0 %	3.16 [0.83, 12.00]
Subtotal (95% CI)	**19**	**12**		**100.0 %**	**3.16 [0.83, 12.00]**
Total events: 10 (IUS), 2 (Medical Rx)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.69 (P = 0.091)					
4 Breast tenderness					
Irvine 1998	14/19	2/12		33.2 %	4.42 [1.21, 16.12]
Kaunitz 2010	4/80	3/82		40.2 %	1.37 [0.32, 5.91]
Reid 2005	6/25	2/26		26.6 %	3.12 [0.69, 14.03]
Subtotal (95% CI)	**124**	**120**		**100.0 %**	**2.85 [1.29, 6.29]**
Total events: 24 (IUS), 7 (Medical Rx)					
Heterogeneity: Chi^2 = 1.42, df = 2 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 2.59 (P = 0.0096)					
5 Nausea					
Reid 2005	2/25	4/26		100.0 %	0.52 [0.10, 2.59]
Subtotal (95% CI)	**25**	**26**		**100.0 %**	**0.52 [0.10, 2.59]**
Total events: 2 (IUS), 4 (Medical Rx)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.80 (P = 0.42)					
6 Diarrhoea					
Reid 2005	1/25	4/26		100.0 %	0.26 [0.03, 2.17]
Subtotal (95% CI)	**25**	**26**		**100.0 %**	**0.26 [0.03, 2.17]**
Total events: 1 (IUS), 4 (Medical Rx)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.24 (P = 0.21)					
7 Upper respiratory infection					
Kaunitz 2010	5/80	1/82		16.8 %	5.13 [0.61, 42.90]
Reid 2005	5/25	5/26		83.2 %	1.04 [0.34, 3.16]
Subtotal (95% CI)	**105**	**108**		**100.0 %**	**1.73 [0.67, 4.44]**
Total events: 10 (IUS), 6 (Medical Rx)					
Heterogeneity: Chi^2 = 1.81, df = 1 (P = 0.18); I^2 =45%					
Test for overall effect: Z = 1.13 (P = 0.26)					
8 Ovarian cysts					
Gupta 2013	1/285	0/286		9.2 %	3.01 [0.12, 73.59]
Kaunitz 2010	10/80	2/82		36.5 %	5.13 [1.16, 22.66]
Reid 2005	6/25	3/26		54.3 %	2.08 [0.58, 7.43]

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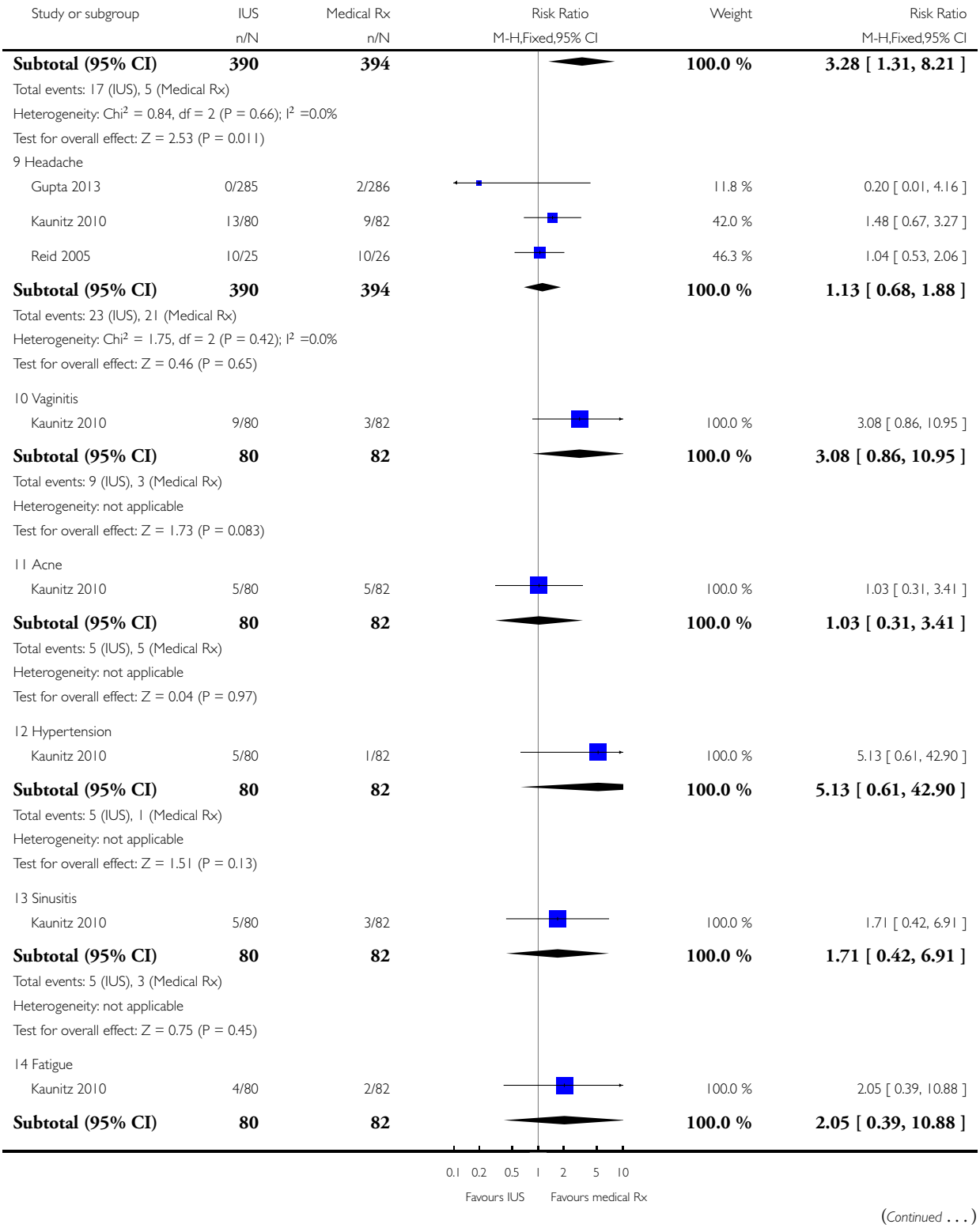

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Study or subgroup	IUS n/N	Medical Rx n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 4 (IUS), 2 (Medical Rx)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.84 (P = 0.40)					
15 Urinary tract infection					
Kaunitz 2010	6/80	3/82		100.0 %	2.05 [0.53, 7.92]
Subtotal (95% CI)	**80**	**82**		**100.0 %**	**2.05 [0.53, 7.92]**
Total events: 6 (IUS), 3 (Medical Rx)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
16 Increased weight					
Kaunitz 2010	4/80	5/82		100.0 %	0.82 [0.23, 2.94]
Subtotal (95% CI)	**80**	**82**		**100.0 %**	**0.82 [0.23, 2.94]**
Total events: 4 (IUS), 5 (Medical Rx)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.30 (P = 0.76)					
17 Lower abdominal pain					
Kaunitz 2010	3/80	5/82		100.0 %	0.62 [0.15, 2.49]
Subtotal (95% CI)	**80**	**82**		**100.0 %**	**0.62 [0.15, 2.49]**
Total events: 3 (IUS), 5 (Medical Rx)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					

Analysis 2.13. Comparison 2 IUS versus any other medical treatment, Outcome 13 Withdrawal from treatment because of adverse events.

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 2 IUS versus any other medical treatment

Outcome: 13 Withdrawal from treatment because of adverse events

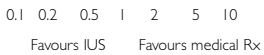
Study or subgroup	IUS n/N	Medical Rx n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gupta 2013	45/285	37/286		84.1 %	1.22 [0.82, 1.83]
Irvine 1998	2/22	5/22		11.4 %	0.40 [0.09, 1.85]
Kaunitz 2010	4/82	2/83		4.5 %	2.02 [0.38, 10.75]
Total (95% CI)	**389**	**391**		**100.0 %**	**1.16 [0.80, 1.69]**

Total events: 51 (IUS), 44 (Medical Rx)

Heterogeneity: Chi^2 = 2.35, df = 2 (P = 0.31); I^2 =15%

Test for overall effect: Z = 0.79 (P = 0.43)

Test for subgroup differences: Not applicable



Analysis 2.14. Comparison 2 IUS versus any other medical treatment, Outcome 14 Withdrawal of treatment for any reason.

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 2 IUS versus any other medical treatment

Outcome: 14 Withdrawal of treatment for any reason

Study or subgroup	LNG IUS n/N	Medical Rx n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gupta 2013	103/285	177/286		100.0 %	0.58 [0.49, 0.70]
Total (95% CI)	**285**	**286**		**100.0 %**	**0.58 [0.49, 0.70]**

Total events: 103 (LNG IUS), 177 (Medical Rx)

Heterogeneity: not applicable

Test for overall effect: Z = 5.89 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 2.15. Comparison 2 IUS versus any other medical treatment, Outcome 15 Failure of treatment.

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 2 IUS versus any other medical treatment

Outcome: 15 Failure of treatment

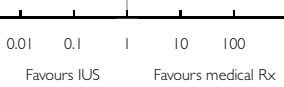
Study or subgroup	IUS n/N	Medical Rx n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kaunitz 2010	12/79	63/81		68.7 %	0.20 [0.11, 0.33]
Sayed 2011	6/26	11/29		11.5 %	0.61 [0.26, 1.41]
Shabaan 2011	6/56	18/56		19.9 %	0.33 [0.14, 0.78]
Total (95% CI)	**161**	**166**		**100.0 %**	**0.27 [0.18, 0.40]**

Total events: 24 (IUS), 92 (Medical Rx)

Heterogeneity: Chi^2 = 5.23, df = 2 (P = 0.07); I^2 =62%

Test for overall effect: Z = 6.56 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 3.1. Comparison 3 IUS versus endometrial ablation, Outcome 1 PBAC score at 12 months.

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 3 IUS versus endometrial ablation

Outcome: 1 PBAC score at 12 months

Study or subgroup	IUS N	Mean(SD)	Ablation N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Malak 2006	26	40.6 (28.5)	30	42.2 (30.4)		-1.60 [-17.04, 13.84]
Soysal 2002	31	55 (11)	35	21.8 (14)		33.20 [27.16, 39.24]

Analysis 3.2. Comparison 3 IUS versus endometrial ablation, Outcome 2 Improvement in HMB within 12 months (amenorrhoea, hypomenorrhoea or eumenorrhoea).

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 3 IUS versus endometrial ablation

Outcome: 2 Improvement in HMB within 12 months (amenorrhoea, hypomenorrhoea or eumenorrhoea)

Study or subgroup	IUS n/N	Endometrial ablation n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Amenorrhoea					
Barrington 2003	3/21	2/23		4.8 %	1.64 [0.30, 8.89]
Crosignani 1997	6/34	9/35		22.3 %	0.69 [0.27, 1.72]
de Souza 2010	3/30	4/28		10.4 %	0.70 [0.17, 2.85]
Ergun 2012	7/18	7/24		15.1 %	1.33 [0.57, 3.12]
Malak 2006	14/26	13/30		30.4 %	1.24 [0.72, 2.14]
Shaw 2007	6/23	1/27		2.3 %	7.04 [0.91, 54.31]
TALIS 2006	6/40	2/39		5.1 %	2.93 [0.63, 13.62]
Tam 2006	0/18	3/15		9.6 %	0.12 [0.01, 2.16]
Subtotal (95% CI)	**210**	**221**		**100.0 %**	**1.21 [0.85, 1.72]**
Total events: 45 (IUS), 41 (Endometrial ablation)					
Heterogeneity: Chi^2 = 8.81, df = 7 (P = 0.27); I^2 =21%					
Test for overall effect: Z = 1.04 (P = 0.30)					
2 Hypomenorrhoea					
Crosignani 1997	16/34	16/35		35.2 %	1.03 [0.62, 1.71]
Ergun 2012	11/18	17/24		32.6 %	0.86 [0.55, 1.35]
Malak 2006	9/26	12/30		24.9 %	0.87 [0.44, 1.72]
Tam 2006	6/18	3/15		7.3 %	1.67 [0.50, 5.56]
Subtotal (95% CI)	**96**	**104**		**100.0 %**	**0.98 [0.73, 1.33]**
Total events: 42 (IUS), 48 (Endometrial ablation)					
Heterogeneity: Chi^2 = 1.22, df = 3 (P = 0.75); I^2 =0.0%					
Test for overall effect: Z = 0.13 (P = 0.90)					
3 Eumenorrhoea					
Crosignani 1997	8/34	7/35		30.8 %	1.18 [0.48, 2.89]
de Souza 2010	0/30	5/28		25.4 %	0.09 [0.00, 1.47]
Tam 2006	4/18	9/15		43.8 %	0.37 [0.14, 0.97]
Subtotal (95% CI)	**82**	**78**		**100.0 %**	**0.55 [0.30, 1.00]**
Total events: 12 (IUS), 21 (Endometrial ablation)					
Heterogeneity: Chi^2 = 5.07, df = 2 (P = 0.08); I^2 =61%					
Test for overall effect: Z = 1.96 (P = 0.050)					

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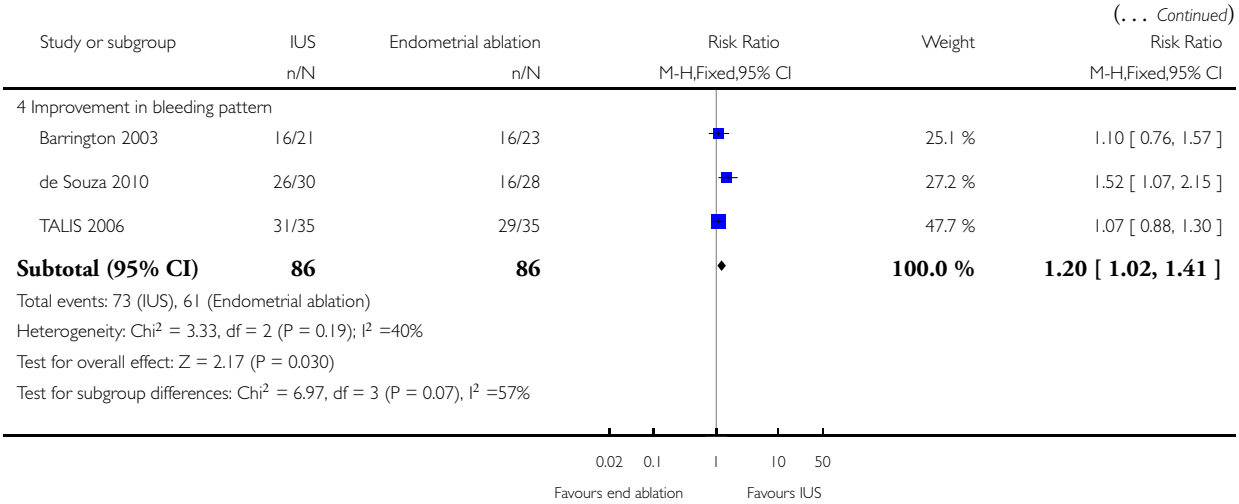

Analysis 3.3. Comparison 3 IUS versus endometrial ablation, Outcome 3 PBAC score after treatment (descriptive results).

PBAC score after treatment (descriptive results)

Study	LNG IUS group	Ablation group	Follow-up	Statistical test	Notes
Barrington 2003	Median = 19, range 0 to 100 n = 21	Median = 27, range 0 to 424 n = 23	6 months	Mann-Whitney test P value 0.69 (no significant difference between groups)	Pre-operative menstrual PBAC scores differed between groups, P value = 0.02
Crosignani 1997	Mean = 38.8, SD = 37.1 n = 30	Mean = 23.5, SD = 32.6 n = 30	12 months	Mann-Whitney U test P value 0.015 favouring ablation	
Ergun 2012	Mean = 70, no measure of variation reported n = 18	Mean = 55, no measure of variation reported n = 24	12 months	Mann Whitney U test No significant difference between groups	
Kittelsen 1998	Median = 7.0 Range = 0 to 101 n = 19	Median = 4.0 Range = 0 to 182 n = 22	36 months	Wilcoxon rank sum test (difference from baseline between groups) P value = 0.86	
Shaw 2007	Median = 26, range 0 to 68 n = 21	Median = 62, range 0 to 142 n = 20	12 months	Mann Whitney test, P < 0.001, favouring LNG IUS	

PBAC score after treatment (descriptive results) (*Continued*)

TALIS 2006	Mean = 20.6 SD = 28.8 n = 37	Mean = 75.4 SD = 91.1 n= 31	24 months	Wilcoxon test, P value = 0.002, favouring LNG IUS	

Analysis 3.4. Comparison 3 IUS versus endometrial ablation, Outcome 4 Proportion of women satisfied with treatment.

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 3 IUS versus endometrial ablation

Outcome: 4 Proportion of women satisfied with treatment

Study or subgroup	IUS n/N	Surgery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Within one year follow-up					
Crosignani 1997	29/34	33/35		25.3 %	0.90 [0.77, 1.06]
Ergun 2012	17/27	22/31		15.9 %	0.89 [0.61, 1.28]
Shaw 2007	20/25	23/28		16.9 %	0.97 [0.75, 1.26]
Soysal 2002	22/32	26/35		19.3 %	0.93 [0.68, 1.25]
TALIS 2006	31/35	29/35		22.6 %	1.07 [0.88, 1.30]
Subtotal (95% CI)	**153**	**164**		**100.0 %**	**0.95 [0.85, 1.07]**
Total events: 119 (IUS), 133 (Surgery)					
Heterogeneity: Chi^2 = 1.97, df = 4 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 0.82 (P = 0.41)					
2 After 1 year and up to 5 years follow-up					
de Souza 2010	27/27	20/25		50.2 %	1.25 [1.01, 1.53]
Shaw 2007	20/24	22/26		49.8 %	0.98 [0.77, 1.26]
Subtotal (95% CI)	**51**	**51**		**100.0 %**	**1.12 [0.95, 1.31]**
Total events: 47 (IUS), 42 (Surgery)					
Heterogeneity: Chi^2 = 2.12, df = 1 (P = 0.15); I^2 =53%					
Test for overall effect: Z = 1.36 (P = 0.17)					

Analysis 3.5. Comparison 3 IUS versus endometrial ablation, Outcome 5 Quality of life (SF36) within 12 months follow-up.

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 3 IUS versus endometrial ablation

Outcome: 5 Quality of life (SF36) within 12 months follow-up

Study or subgroup	LNG IUS N	Mean(SD)	End ablation N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Physical functioning							
Tam 2006	18	40.5 (11)	15	43.6 (12.2)		100.0 %	-3.10 [-11.10, 4.90]
Subtotal (95% CI)	**18**		**15**			**100.0 %**	**-3.10 [-11.10, 4.90]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.76 (P = 0.45)							
2 Role limitation (physical)							
Tam 2006	18	51.1 (10.8)	15	53.6 (9.2)		100.0 %	-2.50 [-9.32, 4.32]
Subtotal (95% CI)	**18**		**15**			**100.0 %**	**-2.50 [-9.32, 4.32]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.72 (P = 0.47)							
3 Bodily pain							
Tam 2006	18	49.5 (10.7)	15	49.1 (9.3)		100.0 %	0.40 [-6.43, 7.23]
Subtotal (95% CI)	**18**		**15**			**100.0 %**	**0.40 [-6.43, 7.23]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.11 (P = 0.91)							
4 General health							
Tam 2006	18	40.5 (8.5)	15	54.9 (14.3)		100.0 %	-14.40 [-22.63, -6.17]
Subtotal (95% CI)	**18**		**15**			**100.0 %**	**-14.40 [-22.63, -6.17]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.43 (P = 0.00061)							
5 Vitality							
Tam 2006	18	42 (7)	15	47.2 (10.6)		100.0 %	-5.20 [-11.46, 1.06]
Subtotal (95% CI)	**18**		**15**			**100.0 %**	**-5.20 [-11.46, 1.06]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.63 (P = 0.10)							
6 Social functioning							
Tam 2006	18	43 (9.3)	15	49.7 (8.6)		100.0 %	-6.70 [-12.82, -0.58]
Subtotal (95% CI)	**18**		**15**			**100.0 %**	**-6.70 [-12.82, -0.58]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.15 (P = 0.032)							
7 Role limitation (emotional)							
Tam 2006	18	46 (11.2)	15	56.1 (9.1)		100.0 %	-10.10 [-17.03, -3.17]

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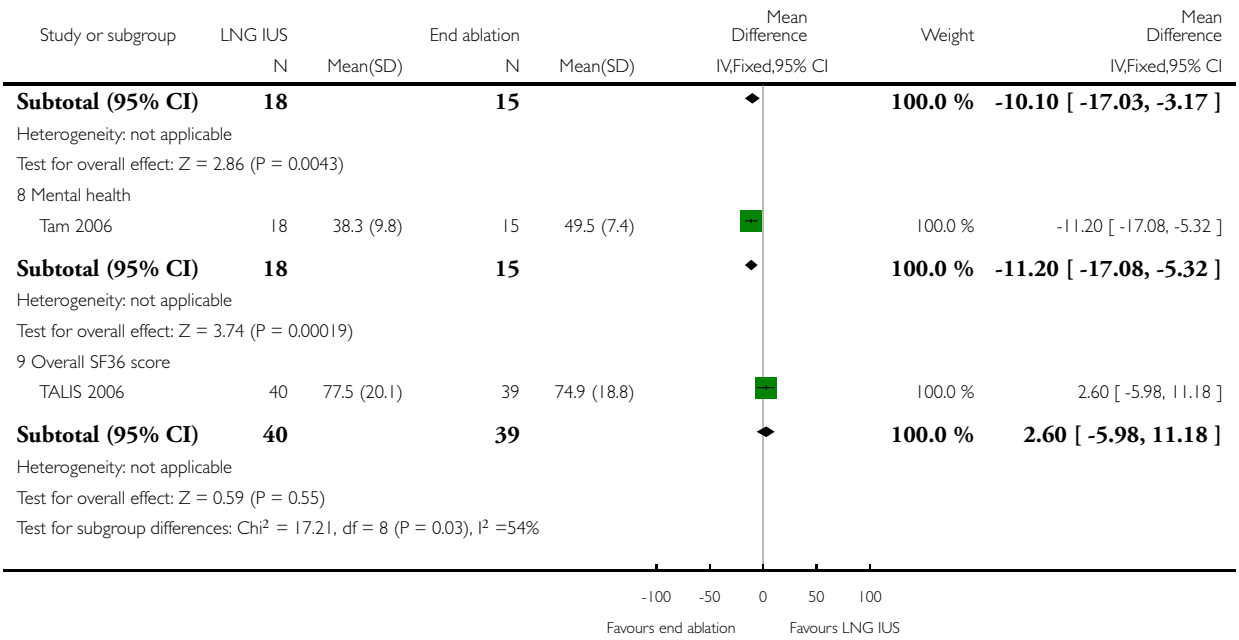


Analysis 3.6. Comparison 3 IUS versus endometrial ablation, Outcome 6 Quality of life (QOL) scores at 12 months (SF36) - descriptive results.

Quality of life (QOL) scores at 12 months (SF36) - descriptive results

Study	SF36 domains	LNG IUS group	Ablation group	Statistical test	Notes
Crosignani 1997	Physical functioning:	Median 85.0, IQR 62.8-95.0	Median 90.0, IQR 71.9-94.7	Mann Whitney U test No statistically significant differences between groups for any domain	
	Social functioning:	Median 75.0, IQR 50.0-87.5	Median 75.0, IQR 56.2-87.5		
	Role limitation (physical):	Median 100.0 IQR 50.0-100.0	Median 100.0 IQR 50.0-100.0		
	Role limitation (emotional):	Median 66.7, IQR 33.3-100.0	Median 100.0 IQR 66.7-100.0		
	Bodily pain:	Median 41, IQR 41.0-84.0	Median 72.0, IQR 55.0-92.0		
	General health perception:	Median 65.0, IQR 51.0-79.5	Median 72.5, IQR 64.5-77.0		
	Vitality:				

Quality of life (QOL) scores at 12 months (SF36) - descriptive results (*Continued*)

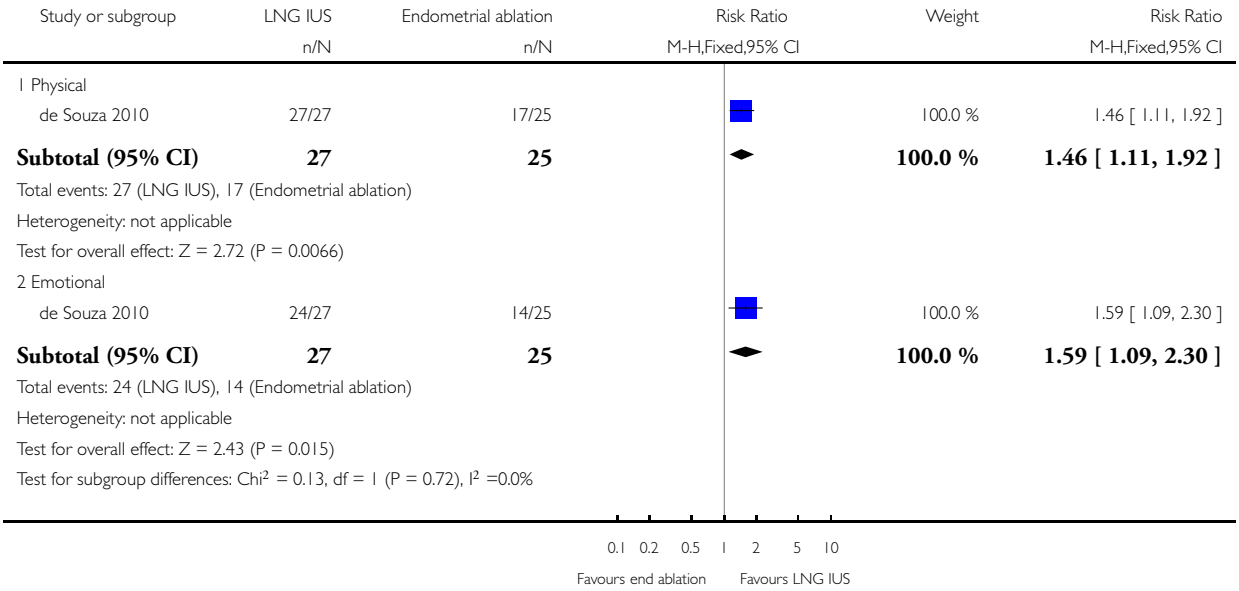
	Mental health:	Median 55.0, IQR 47.5-65.0 Median 60.0, IQR 46.0-68.0	Median 55.0, IQR 40.0-70.0 Median 64.0, IQR 46.7-68.0		
Soysal 2002	Physical functioning: Social functioning: Role limitation (physical): Role limitation (emotional) Pain: General health perception Vitality: Mental health:	Median: 72.5, IQR 53.7 to 91.2 Median 50, IQR 3.7 to 96.8 Median 25, IQR -25 to 75 Median 33.3, IQR -58.3 to 124.9 Median 51, IQR 30 to 72 Median 52, IQR 25.5 to 78.5 Median 45, IQR 26.2 to 63.7 Median 52, IQR 25 to 79	Median: 75, IQR 42.5 to 40 Median 50, IQR 125 to 87.5 Median 50, IQR -25 to 125 Median 33.3, IQR -33.3 to 99.9 Median 51, IQR 20 to 82 Median 47, IQR 19.5 to 74.5 Median 45, IQR 10 to 80 Median 52, IQR 22 to 82	Mann Whitney U test No significant differences between groups for any domain, except for role limitations due to physical functioning: Mean difference 20.22 (1.98 to 38.45)	

Analysis 3.7. Comparison 3 IUS versus endometrial ablation, Outcome 7 Quality of life within 5 years follow-up (proportion with improved wellbeing).

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 3 IUS versus endometrial ablation

Outcome: 7 Quality of life within 5 years follow-up (proportion with improved wellbeing)



Analysis 3.8. Comparison 3 IUS versus endometrial ablation, Outcome 8 Quality of life within 5 years - psychological wellbeing (continuous).

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 3 IUS versus endometrial ablation

Outcome: 8 Quality of life within 5 years - psychological wellbeing (continuous)

Study or subgroup	LNG IUS N	Mean(SD)	End ablation N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
de Souza 2010	17	100.4 (23.9)	11	90.1 (20.19)		100.0 %	10.30 [-6.18, 26.78]
Total (95% CI)	**17**		**11**			**100.0 %**	**10.30 [-6.18, 26.78]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.23 (P = 0.22)

Test for subgroup differences: Not applicable

Analysis 3.9. Comparison 3 IUS versus endometrial ablation, Outcome 9 Total proportion of women with side effects.

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 3 IUS versus endometrial ablation

Outcome: 9 Total proportion of women with side effects

Study or subgroup	IUS n/N	Ablation n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Crosignani 1997	19/34	9/35		31.8 %	2.17 [1.15, 4.11]
Malak 2006	17/30	11/30		39.5 %	1.55 [0.88, 2.72]
Soysal 2002	21/36	8/36		28.7 %	2.63 [1.34, 5.13]
Total (95% CI)	**100**	**101**		**100.0 %**	**2.06 [1.44, 2.94]**

Total events: 57 (IUS), 28 (Ablation)

Heterogeneity: Chi^2 = 1.52, df = 2 (P = 0.47); I^2 =0.0%

Test for overall effect: Z = 3.94 (P = 0.000081)

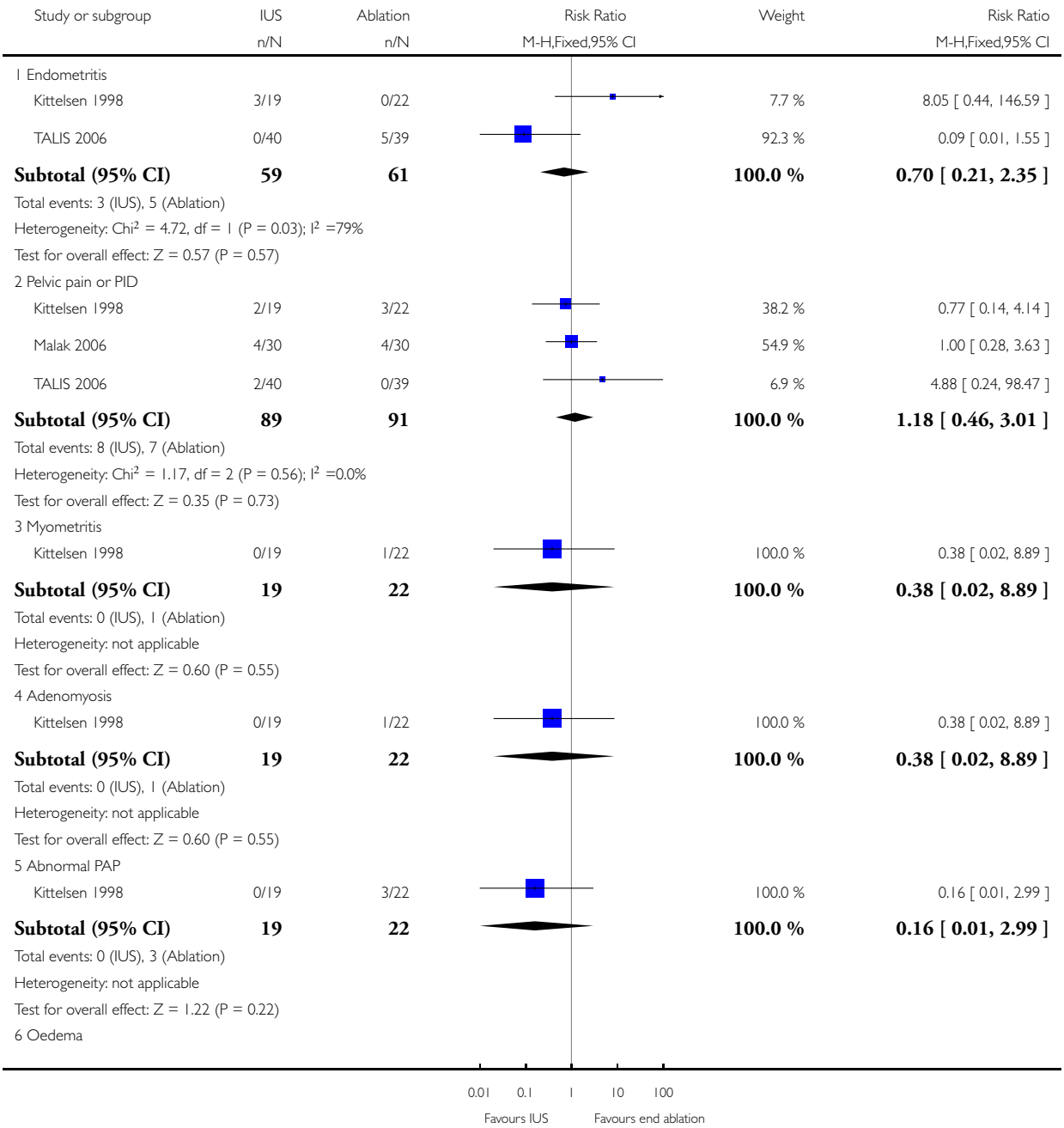
Test for subgroup differences: Not applicable

Analysis 3.10. Comparison 3 IUS versus endometrial ablation, Outcome 10 Individual side effects.

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 3 IUS versus endometrial ablation

Outcome: 10 Individual side effects



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Study or subgroup	IUS n/N	Ablation n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kittelsen 1998	1/19	0/22		100.0 %	3.45 [0.15, 80.03]
Subtotal (95% CI)	**19**	**22**		**100.0 %**	**3.45 [0.15, 80.03]**
Total events: 1 (IUS), 0 (Ablation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.77 (P = 0.44)					
7 Breast pain					
Crosignani 1997	6/34	0/35		24.7 %	13.37 [0.78, 228.53]
Malak 2006	3/30	0/30		25.1 %	7.00 [0.38, 129.93]
Soysal 2002	5/36	1/36		50.2 %	5.00 [0.61, 40.70]
Subtotal (95% CI)	**100**	**101**		**100.0 %**	**7.57 [1.78, 32.23]**
Total events: 14 (IUS), 1 (Ablation)					
Heterogeneity: Chi^2 = 0.31, df = 2 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 2.74 (P = 0.0062)					
8 Weight gain					
Crosignani 1997	8/34	3/35		42.5 %	2.75 [0.79, 9.49]
Soysal 2002	10/36	4/36		57.5 %	2.50 [0.86, 7.24]
Subtotal (95% CI)	**70**	**71**		**100.0 %**	**2.60 [1.16, 5.84]**
Total events: 18 (IUS), 7 (Ablation)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 2.32 (P = 0.020)					
9 Mood swings					
Malak 2006	1/30	0/30		33.3 %	3.00 [0.13, 70.83]
Soysal 2002	2/36	1/36		66.7 %	2.00 [0.19, 21.09]
Subtotal (95% CI)	**66**	**66**		**100.0 %**	**2.33 [0.36, 15.32]**
Total events: 3 (IUS), 1 (Ablation)					
Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 0.88 (P = 0.38)					
10 Bloating					
Crosignani 1997	10/34	2/35		49.6 %	5.15 [1.22, 21.79]
Soysal 2002	8/36	2/36		50.4 %	4.00 [0.91, 17.55]
Subtotal (95% CI)	**70**	**71**		**100.0 %**	**4.57 [1.63, 12.82]**
Total events: 18 (IUS), 4 (Ablation)					
Heterogeneity: Chi^2 = 0.06, df = 1 (P = 0.81); I^2 =0.0%					
Test for overall effect: Z = 2.89 (P = 0.0039)					
11 Acne or greasy skin					
Crosignani 1997	2/34	0/35		33.0 %	5.14 [0.26, 103.35]
Malak 2006	2/30	0/30		33.5 %	5.00 [0.25, 99.95]
Soysal 2002	7/36	0/36		33.5 %	15.00 [0.89, 253.22]

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Study or subgroup	IUS n/N	Ablation n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**100**	**101**		**100.0 %**	**8.40 [1.57, 44.76]**
Total events: 11 (IUS), 0 (Ablation)					
Heterogeneity: Chi² = 0.38, df = 2 (P = 0.83); I² =0.0%					
Test for overall effect: Z = 2.49 (P = 0.013)					
12 Nausea					
Soysal 2002	4/36	0/36		100.0 %	9.00 [0.50, 161.29]
Subtotal (95% CI)	**36**	**36**		**100.0 %**	**9.00 [0.50, 161.29]**
Total events: 4 (IUS), 0 (Ablation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.49 (P = 0.14)					
13 Headache					
Crosignani 1997	4/34	3/35		74.7 %	1.37 [0.33, 5.68]
Malak 2006	2/30	0/30		12.6 %	5.00 [0.25, 99.95]
Soysal 2002	1/36	0/36		12.6 %	3.00 [0.13, 71.28]
Subtotal (95% CI)	**100**	**101**		**100.0 %**	**2.04 [0.64, 6.50]**
Total events: 7 (IUS), 3 (Ablation)					
Heterogeneity: Chi² = 0.70, df = 2 (P = 0.70); I² =0.0%					
Test for overall effect: Z = 1.20 (P = 0.23)					
14 Leg pain					
Crosignani 1997	1/34	0/35		49.6 %	3.09 [0.13, 73.21]
Soysal 2002	1/36	0/36		50.4 %	3.00 [0.13, 71.28]
Subtotal (95% CI)	**70**	**71**		**100.0 %**	**3.04 [0.32, 28.57]**
Total events: 2 (IUS), 0 (Ablation)					
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² =0.0%					
Test for overall effect: Z = 0.97 (P = 0.33)					
15 Dysmenorrhoea					
Soysal 2002	0/36	2/36		62.2 %	0.20 [0.01, 4.03]
TALIS 2006	0/40	1/39		37.8 %	0.33 [0.01, 7.75]
Subtotal (95% CI)	**76**	**75**		**100.0 %**	**0.25 [0.03, 2.17]**
Total events: 0 (IUS), 3 (Ablation)					
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.83); I² =0.0%					
Test for overall effect: Z = 1.26 (P = 0.21)					
16 Lower abdominal pain					
Crosignani 1997	2/34	1/35		20.2 %	2.06 [0.20, 21.67]
Kittelsen 1998	0/19	1/22		28.6 %	0.38 [0.02, 8.89]
Malak 2006	5/30	1/30		20.5 %	5.00 [0.62, 40.28]
Soysal 2002	0/36	1/36		30.7 %	0.33 [0.01, 7.92]
Subtotal (95% CI)	**119**	**123**		**100.0 %**	**1.65 [0.55, 4.97]**

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Study or subgroup	IUS n/N	Ablation n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 7 (IUS), 4 (Ablation)					
Heterogeneity: Chi² = 2.93, df = 3 (P = 0.40); I² =0.0%					
Test for overall effect: Z = 0.89 (P = 0.37)					
17 Actinomycoses					
TALIS 2006	1/40	0/39		100.0 %	2.93 [0.12, 69.74]
Subtotal (95% CI)	**40**	**39**		**100.0 %**	**2.93 [0.12, 69.74]**
Total events: 1 (IUS), 0 (Ablation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
18 Decreased libido					
Crosignani 1997	2/34	2/35		100.0 %	1.03 [0.15, 6.90]
Subtotal (95% CI)	**34**	**35**		**100.0 %**	**1.03 [0.15, 6.90]**
Total events: 2 (IUS), 2 (Ablation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.98)					
19 Hair loss					
Crosignani 1997	2/34	0/35		100.0 %	5.14 [0.26, 103.35]
Subtotal (95% CI)	**34**	**35**		**100.0 %**	**5.14 [0.26, 103.35]**
Total events: 2 (IUS), 0 (Ablation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.07 (P = 0.28)					
20 Anxiety or depression					
Crosignani 1997	2/34	1/35		100.0 %	2.06 [0.20, 21.67]
Subtotal (95% CI)	**34**	**35**		**100.0 %**	**2.06 [0.20, 21.67]**
Total events: 2 (IUS), 1 (Ablation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.60 (P = 0.55)					
21 Hypertension					
Crosignani 1997	1/34	0/35		100.0 %	3.09 [0.13, 73.21]
Subtotal (95% CI)	**34**	**35**		**100.0 %**	**3.09 [0.13, 73.21]**
Total events: 1 (IUS), 0 (Ablation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.49)					
22 Endometriosis					
Kittelsen 1998	0/19	1/22		100.0 %	0.38 [0.02, 8.89]
Subtotal (95% CI)	**19**	**22**		**100.0 %**	**0.38 [0.02, 8.89]**
Total events: 0 (IUS), 1 (Ablation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.60 (P = 0.55)					

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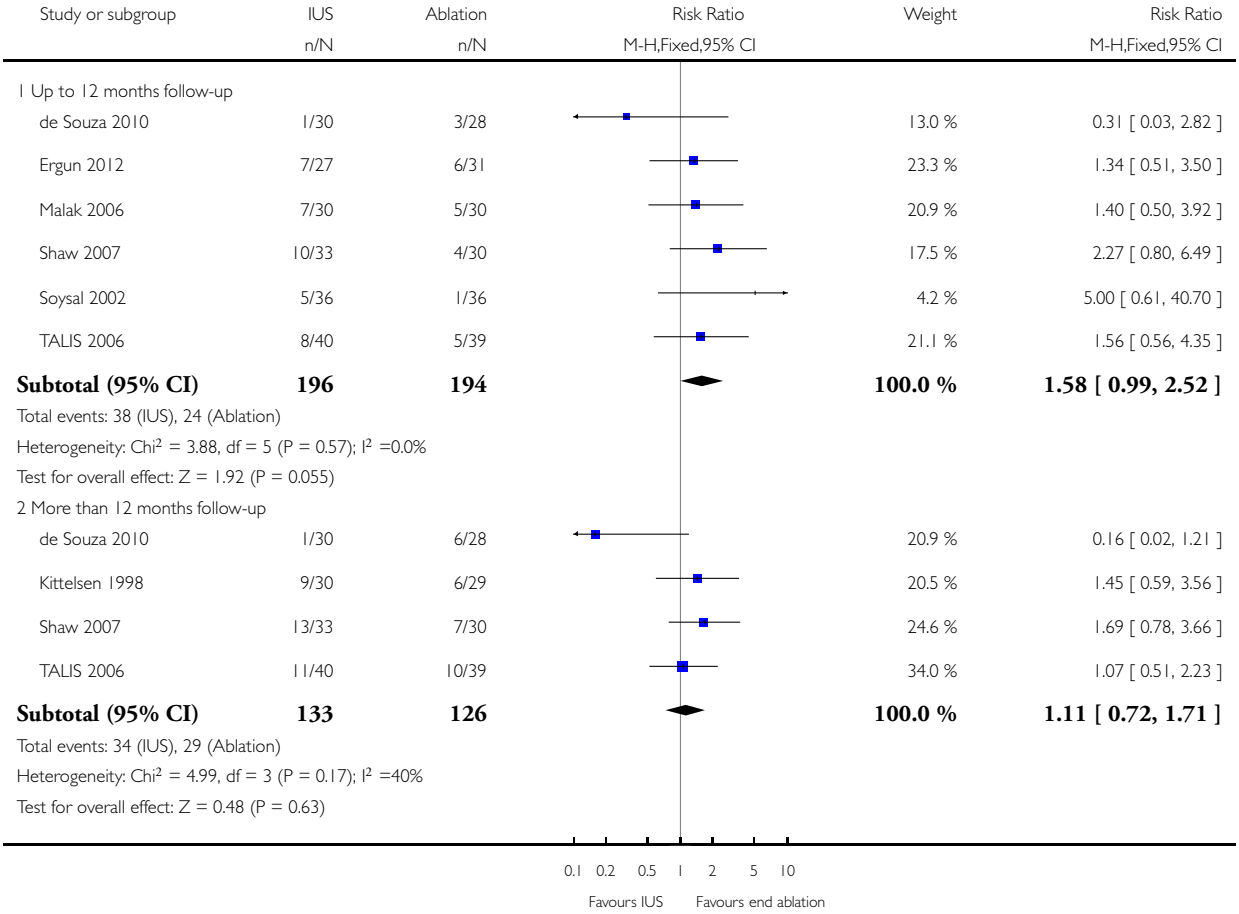
Study or subgroup	IUS n/N	Ablation n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
23 Bleeding or spotting					
Malak 2006	5/30	5/30		33.1 %	1.00 [0.32, 3.10]
Soysal 2002	6/36	0/36		3.3 %	13.00 [0.76, 222.53]
TALIS 2006	4/40	9/39		60.3 %	0.43 [0.15, 1.29]
Tam 2006	5/15	0/15		3.3 %	11.00 [0.66, 182.87]
Subtotal (95% CI)	**121**	**120**		**100.0 %**	**1.39 [0.74, 2.58]**
Total events: 20 (IUS), 14 (Ablation)					
Heterogeneity: Chi^2 = 9.15, df = 3 (P = 0.03); I^2 =67%					
Test for overall effect: Z = 1.03 (P = 0.30)					
24 Hematometra					
Malak 2006	0/30	1/30		100.0 %	0.33 [0.01, 7.87]
Subtotal (95% CI)	**30**	**30**		**100.0 %**	**0.33 [0.01, 7.87]**
Total events: 0 (IUS), 1 (Ablation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					
25 Vaginitis					
Malak 2006	4/30	2/30		100.0 %	2.00 [0.40, 10.11]
Subtotal (95% CI)	**30**	**30**		**100.0 %**	**2.00 [0.40, 10.11]**
Total events: 4 (IUS), 2 (Ablation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.84 (P = 0.40)					
26 Genital ulceration					
Malak 2006	0/30	1/30		100.0 %	0.33 [0.01, 7.87]
Subtotal (95% CI)	**30**	**30**		**100.0 %**	**0.33 [0.01, 7.87]**
Total events: 0 (IUS), 1 (Ablation)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.68 (P = 0.50)					

Analysis 3.11. Comparison 3 IUS versus endometrial ablation, Outcome 11 Treatment failure.

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 3 IUS versus endometrial ablation

Outcome: 11 Treatment failure



Analysis 3.12. Comparison 3 IUS versus endometrial ablation, Outcome 12 Total cost per woman.

Total cost per woman

Study	Details of cost	LNG IUS: Mean cost	Ablation: Mean cost	Comments
TALIS 2006	Expected cost	Mean = NZD 1241	Mean = NZD 2418	Economic modelling examined the expected cost and outcome for women entering treatment (costs of procedure, recovery, medications, equipment, GP, lost income and failed treatment)

Analysis 4.1. Comparison 4 IUS versus hysterectomy, Outcome 1 PBAC score (at 12 months follow-up).

PBAC score (at 12 months follow-up)

Study	LNG IUS group	Laparoscopic supracervical hysterectomy group	Statistical test, results	Notes
At 12 months follow-up				
Sesti 2012	Mean = 3.5, SD = 16.0, n= 36	Mean = 3.7, SD = 3.0, n=36	Fisher's exact test, no significant difference between groups	
At 24 months follow-up				
Sesti 2012	Mean = 56.4, SD = 72.8, n= 36	Mean = 3.74, SD = 3.05, n= 36	Fisher's exact test, P < 0.001	

Analysis 4.2. Comparison 4 IUS versus hysterectomy, Outcome 2 Satisfaction with treatment (5 years follow-up).

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 4 IUS versus hysterectomy

Outcome: 2 Satisfaction with treatment (5 years follow-up)

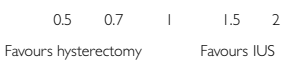
Study or subgroup	IUS n/N	Hysterectomy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hurskainen 2001	110/117	107/115		100.0 %	1.01 [0.94, 1.08]
Total (95% CI)	**117**	**115**		**100.0 %**	**1.01 [0.94, 1.08]**

Total events: 110 (IUS), 107 (Hysterectomy)

Heterogeneity: not applicable

Test for overall effect: Z = 0.30 (P = 0.76)

Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4 IUS versus hysterectomy, Outcome 3 Quality of life scores at 12 months follow-up (descriptive data).

Quality of life scores at 12 months follow-up (descriptive data)

Study	Outcome	LNG IUS	Hysterectomy	Statistical test, results	Notes
Ozdegirmenci 2011	WHOQOL-BREF TR: Physical Psychological Social Environmental	n = 43 Median = 68, IQR 59 to 77 Median = 58, IQR 51 to 66 Median = 67, IQR 59 to 75 Mean = 62, SD = 15	n = 32 Median = 72, IQR 57 to 84 Median = 62, IQR 50 to 75 Median = 67, IQR 55 to 78 Mean = 68, SD = 13	Mann Whitney U test, no difference between groups Student's T test, no difference between groups	

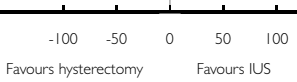
Analysis 4.4. Comparison 4 IUS versus hysterectomy, Outcome 4 Quality of life scores at end of study (final values).

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 4 IUS versus hysterectomy

Outcome: 4 Quality of life scores at end of study (final values)

Study or subgroup	IUS N	Mean(SD)	Hysterectomy N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 SF36: General health							
Sesti 2012	36	87.4 (13.5)	36	88.2 (8.6)		100.0 %	-0.80 [-6.03, 4.43]
Subtotal (95% CI)	**36**		**36**			**100.0 %**	**-0.80 [-6.03, 4.43]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.30 (P = 0.76)							
2 SF36: Physical function							
Sesti 2012	36	85.3 (15.6)	36	90.3 (8.3)		100.0 %	-5.00 [-10.77, 0.77]
Subtotal (95% CI)	**36**		**36**			**100.0 %**	**-5.00 [-10.77, 0.77]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.70 (P = 0.090)							
3 SF36: Role (physical)							
Sesti 2012	36	86.8 (12.9)	36	88.8 (9.4)		100.0 %	-2.00 [-7.21, 3.21]
Subtotal (95% CI)	**36**		**36**			**100.0 %**	**-2.00 [-7.21, 3.21]**
Heterogeneity: not applicable							



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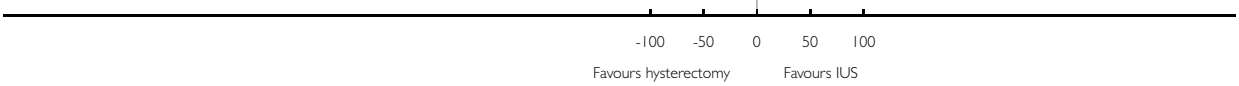
Study or subgroup	IUS N	Mean(SD)	Hysterectomy N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Test for overall effect: Z = 0.75 (P = 0.45)							
4 SF36: Role (emotional)							
Sesti 2012	36	83.5 (16.4)	36	67.4 (14.8)		100.0 %	16.10 [8.88, 23.32]
Subtotal (95% CI)	**36**		**36**			**100.0 %**	**16.10 [8.88, 23.32]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.37 (P = 0.000012)							
5 SF36: Mental health							
Sesti 2012	36	85.3 (15.6)	36	48.5 (12)		100.0 %	36.80 [30.37, 43.23]
Subtotal (95% CI)	**36**		**36**			**100.0 %**	**36.80 [30.37, 43.23]**
Heterogeneity: not applicable							
Test for overall effect: Z = 11.22 (P < 0.00001)							
6 SF36: Social function							
Sesti 2012	36	89.4 (12.7)	36	87.6 (16.5)		100.0 %	1.80 [-5.00, 8.60]
Subtotal (95% CI)	**36**		**36**			**100.0 %**	**1.80 [-5.00, 8.60]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.52 (P = 0.60)							
7 SF36: Vitality							
Sesti 2012	36	78.8 (14)	36	73.2 (13.6)		100.0 %	5.60 [-0.78, 11.98]
Subtotal (95% CI)	**36**		**36**			**100.0 %**	**5.60 [-0.78, 11.98]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.72 (P = 0.085)							
8 SF36: Pain							
Sesti 2012	36	59.9 (12.4)	36	74.7 (22.9)		100.0 %	-14.80 [-23.31, -6.29]
Subtotal (95% CI)	**36**		**36**			**100.0 %**	**-14.80 [-23.31, -6.29]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.41 (P = 0.00065)							
Test for subgroup differences: Chi^2 = 147.70, df = 7 (P = 0.00), I^2 =95%							



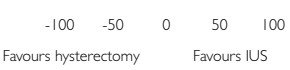
Analysis 4.5. Comparison 4 IUS versus hysterectomy, Outcome 5 Quality of life scores at end of study (change values).

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 4 IUS versus hysterectomy

Outcome: 5 Quality of life scores at end of study (change values)

Study or subgroup	IUS N	Mean(SD)	Hysterectomy N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 EQ-5D							
Hurskainen 2001	110	-1.1 (0.21)	111	-0.01 (0.22)		100.0 %	-1.09 [-1.15, -1.03]
Subtotal (95% CI)	**110**		**111**			**100.0 %**	**-1.09 [-1.15, -1.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 37.68 (P < 0.00001)							
2 SF36: General health							
Hurskainen 2001	110	-2.3 (18.73)	111	-4.5 (20.16)		100.0 %	2.20 [-2.93, 7.33]
Subtotal (95% CI)	**110**		**111**			**100.0 %**	**2.20 [-2.93, 7.33]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.84 (P = 0.40)							
3 SF36: Physical functioning							
Hurskainen 2001	110	-3.4 (22.21)	111	-3.8 (22.58)		100.0 %	0.40 [-5.51, 6.31]
Subtotal (95% CI)	**110**		**111**			**100.0 %**	**0.40 [-5.51, 6.31]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.13 (P = 0.89)							
4 SF36: Emotional wellbeing							
Hurskainen 2001	110	5.7 (23.54)	111	3.2 (20.7)		100.0 %	2.50 [-3.35, 8.35]
Subtotal (95% CI)	**110**		**111**			**100.0 %**	**2.50 [-3.35, 8.35]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.84 (P = 0.40)							
5 SF36: Social functioning							
Hurskainen 2001	110	7.9 (29.7)	111	1.8 (27.68)		100.0 %	6.10 [-1.47, 13.67]
Subtotal (95% CI)	**110**		**111**			**100.0 %**	**6.10 [-1.47, 13.67]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.58 (P = 0.11)							
6 SF36: Energy/vitality							
Hurskainen 2001	110	6 (23)	111	5.3 (25.26)		100.0 %	0.70 [-5.67, 7.07]
Subtotal (95% CI)	**110**		**111**			**100.0 %**	**0.70 [-5.67, 7.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.22 (P = 0.83)							
7 SF36: Pain							
Hurskainen 2001	110	4.4 (25.69)	111	4 (32.52)		100.0 %	0.40 [-7.32, 8.12]



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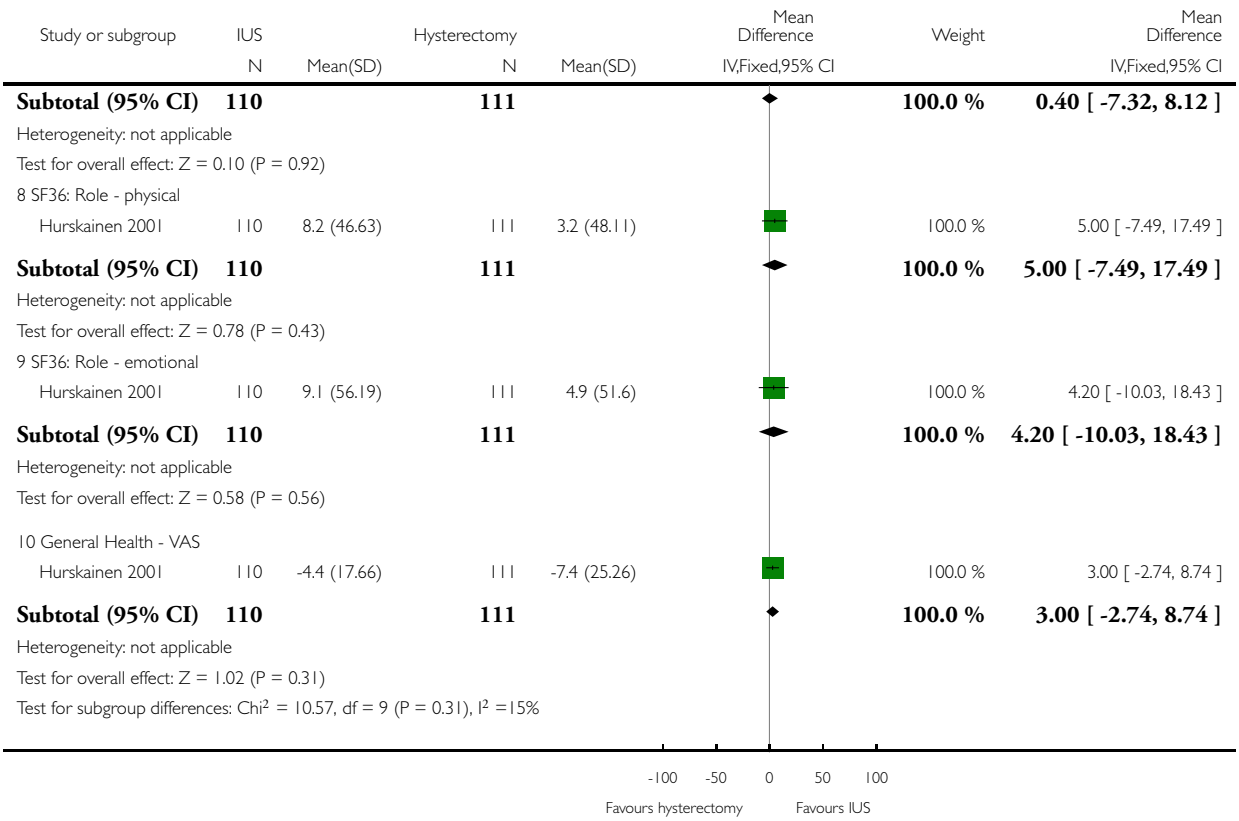
Study or subgroup	IUS N	Mean(SD)	Hysterectomy N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Subtotal (95% CI)	**110**		**111**			**100.0 %**	**0.40 [-7.32, 8.12]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.10 (P = 0.92)							
8 SF36: Role - physical							
Hurskainen 2001	110	8.2 (46.63)	111	3.2 (48.11)		100.0 %	5.00 [-7.49, 17.49]
Subtotal (95% CI)	**110**		**111**			**100.0 %**	**5.00 [-7.49, 17.49]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.78 (P = 0.43)							
9 SF36: Role - emotional							
Hurskainen 2001	110	9.1 (56.19)	111	4.9 (51.6)		100.0 %	4.20 [-10.03, 18.43]
Subtotal (95% CI)	**110**		**111**			**100.0 %**	**4.20 [-10.03, 18.43]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.58 (P = 0.56)							
10 General Health - VAS							
Hurskainen 2001	110	-4.4 (17.66)	111	-7.4 (25.26)		100.0 %	3.00 [-2.74, 8.74]
Subtotal (95% CI)	**110**		**111**			**100.0 %**	**3.00 [-2.74, 8.74]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.02 (P = 0.31)							
Test for subgroup differences: Chi^2 = 10.57, df = 9 (P = 0.31), I^2 =15%							



Analysis 4.6. Comparison 4 IUS versus hysterectomy, Outcome 6 Early adverse events.

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 4 IUS versus hysterectomy

Outcome: 6 Early adverse events

Study or subgroup	IUS n/N	Hysterectomy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Headache					
Ozdegirmenci 2011	5/43	0/43		100.0 %	11.00 [0.63, 192.99]
Subtotal (95% CI)	**43**	**43**		**100.0 %**	**11.00 [0.63, 192.99]**
Total events: 5 (IUS), 0 (Hysterectomy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.64 (P = 0.10)					
2 Breast tenderness					
Ozdegirmenci 2011	3/43	0/43		100.0 %	7.00 [0.37, 131.56]
Subtotal (95% CI)	**43**	**43**		**100.0 %**	**7.00 [0.37, 131.56]**
Total events: 3 (IUS), 0 (Hysterectomy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.19)					
3 Acne					
Ozdegirmenci 2011	2/43	0/43		100.0 %	5.00 [0.25, 101.18]
Subtotal (95% CI)	**43**	**43**		**100.0 %**	**5.00 [0.25, 101.18]**
Total events: 2 (IUS), 0 (Hysterectomy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					
4 Depressive episode					
Hurskainen 2001	2/117	0/115		50.2 %	4.92 [0.24, 101.28]
Ozdegirmenci 2011	1/43	0/43		49.8 %	3.00 [0.13, 71.65]
Subtotal (95% CI)	**160**	**158**		**100.0 %**	**3.96 [0.45, 35.06]**
Total events: 3 (IUS), 0 (Hysterectomy)					
Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.82); I^2 =0.0%					
Test for overall effect: Z = 1.24 (P = 0.22)					
5 Wound infection					
Hurskainen 2001	2/117	12/115		87.6 %	0.16 [0.04, 0.72]
Ozdegirmenci 2011	0/43	1/32		12.4 %	0.25 [0.01, 5.94]
Subtotal (95% CI)	**160**	**147**		**100.0 %**	**0.17 [0.05, 0.66]**
Total events: 2 (IUS), 13 (Hysterectomy)					
Heterogeneity: Chi^2 = 0.06, df = 1 (P = 0.81); I^2 =0.0%					
Test for overall effect: Z = 2.56 (P = 0.010)					
6 Infected pelvic haematoma					
Hurskainen 2001	9/117	6/115		100.0 %	1.47 [0.54, 4.01]

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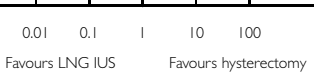
Study or subgroup	IUS n/N	Hysterectomy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**117**	**115**		**100.0 %**	**1.47 [0.54, 4.01]**
Total events: 9 (IUS), 6 (Hysterectomy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.76 (P = 0.45)					
7 Postoperative fever					
Hurskainen 2001	1/117	2/115		100.0 %	0.49 [0.05, 5.35]
Subtotal (95% CI)	**117**	**115**		**100.0 %**	**0.49 [0.05, 5.35]**
Total events: 1 (IUS), 2 (Hysterectomy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.58 (P = 0.56)					
8 Urinary retention					
Hurskainen 2001	1/117	4/115		100.0 %	0.25 [0.03, 2.17]
Subtotal (95% CI)	**117**	**115**		**100.0 %**	**0.25 [0.03, 2.17]**
Total events: 1 (IUS), 4 (Hysterectomy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.26 (P = 0.21)					
9 Bladder perforation					
Hurskainen 2001	0/117	3/115		100.0 %	0.14 [0.01, 2.69]
Subtotal (95% CI)	**117**	**115**		**100.0 %**	**0.14 [0.01, 2.69]**
Total events: 0 (IUS), 3 (Hysterectomy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.19)					
10 Bowel perforation					
Hurskainen 2001	0/117	1/115		100.0 %	0.33 [0.01, 7.96]
Subtotal (95% CI)	**117**	**115**		**100.0 %**	**0.33 [0.01, 7.96]**
Total events: 0 (IUS), 1 (Hysterectomy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
11 Wound rupture					
Hurskainen 2001	0/117	2/115		100.0 %	0.20 [0.01, 4.05]
Subtotal (95% CI)	**117**	**115**		**100.0 %**	**0.20 [0.01, 4.05]**
Total events: 0 (IUS), 2 (Hysterectomy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.05 (P = 0.29)					
12 Peritonitis					
Hurskainen 2001	0/117	1/115		100.0 %	0.33 [0.01, 7.96]
Subtotal (95% CI)	**117**	**115**		**100.0 %**	**0.33 [0.01, 7.96]**
Total events: 0 (IUS), 1 (Hysterectomy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
13 Ileus					



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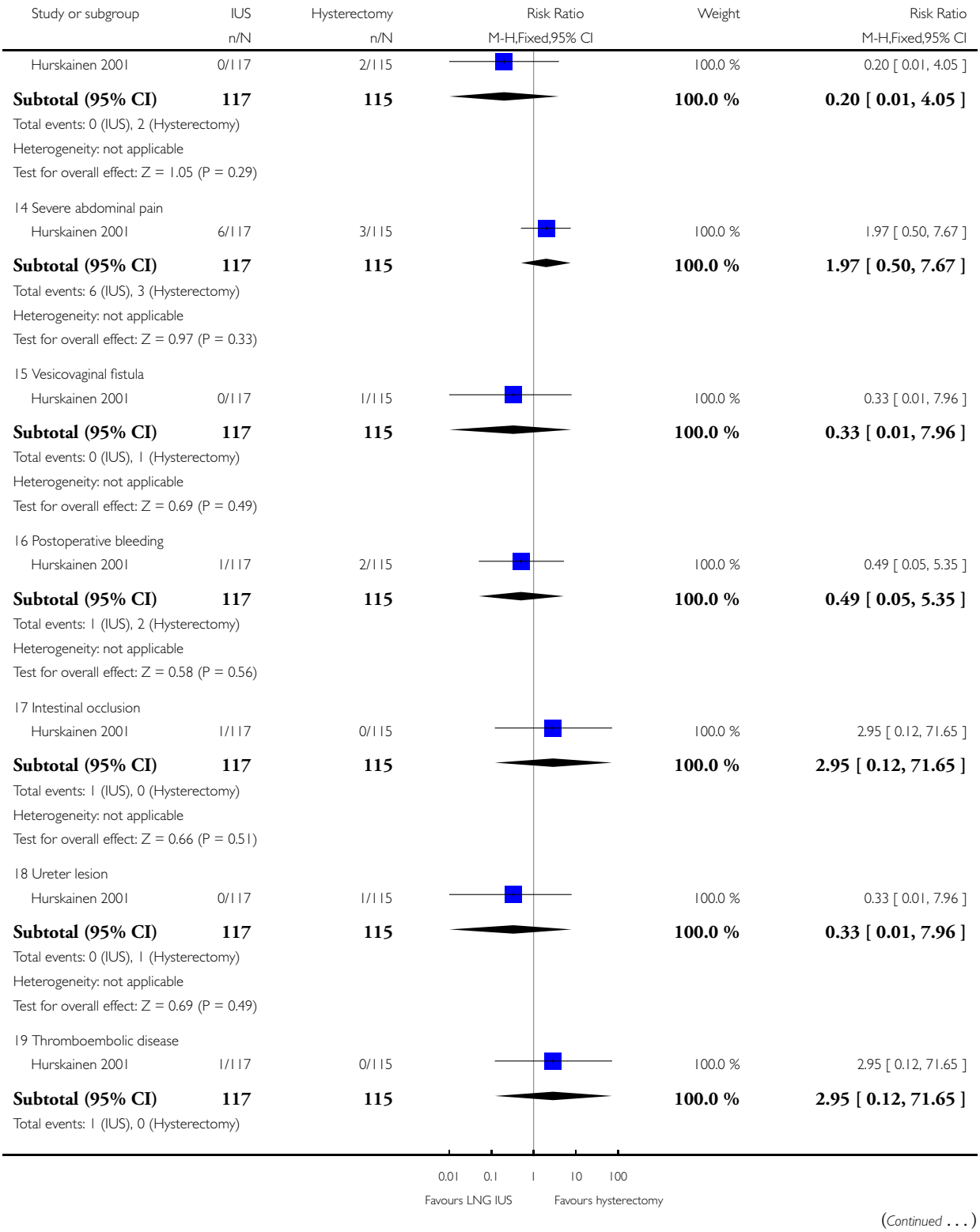

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Study or subgroup	IUS n/N	Hysterectomy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 0.66 (P = 0.51)					
Test for subgroup differences: Chi^2 = 23.72, df = 18 (P = 0.16), I^2 =24%					

0.01 0.1 1 10 100

Favours LNG IUS Favours hysterectomy

Analysis 4.7. Comparison 4 IUS versus hysterectomy, Outcome 7 Later adverse events.

Review: Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding

Comparison: 4 IUS versus hysterectomy

Outcome: 7 Later adverse events

Study or subgroup	IUS n/N	Hysterectomy n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Back pain (increase from baseline)					
Hurskainen 2001	36/117	61/115		100.0 %	0.58 [0.42, 0.80]
Subtotal (95% CI)	**117**	**115**		**100.0 %**	**0.58 [0.42, 0.80]**
Total events: 36 (IUS), 61 (Hysterectomy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.32 (P = 0.00090)					
2 Abdominal pain (increase from baseline)					
Hurskainen 2001	11/117	18/115		100.0 %	0.60 [0.30, 1.22]
Subtotal (95% CI)	**117**	**115**		**100.0 %**	**0.60 [0.30, 1.22]**
Total events: 11 (IUS), 18 (Hysterectomy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.42 (P = 0.16)					
3 Urge incontinence					
Hurskainen 2001	11/68	34/153		100.0 %	0.73 [0.39, 1.35]
Subtotal (95% CI)	**68**	**153**		**100.0 %**	**0.73 [0.39, 1.35]**
Total events: 11 (IUS), 34 (Hysterectomy)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.01 (P = 0.31)					
4 Stress incontinence					
Hurskainen 2001	23/68	74/153		100.0 %	0.70 [0.48, 1.01]

0.01 0.1 1 10 100

Favours LNG IUS Favours hysterectomy

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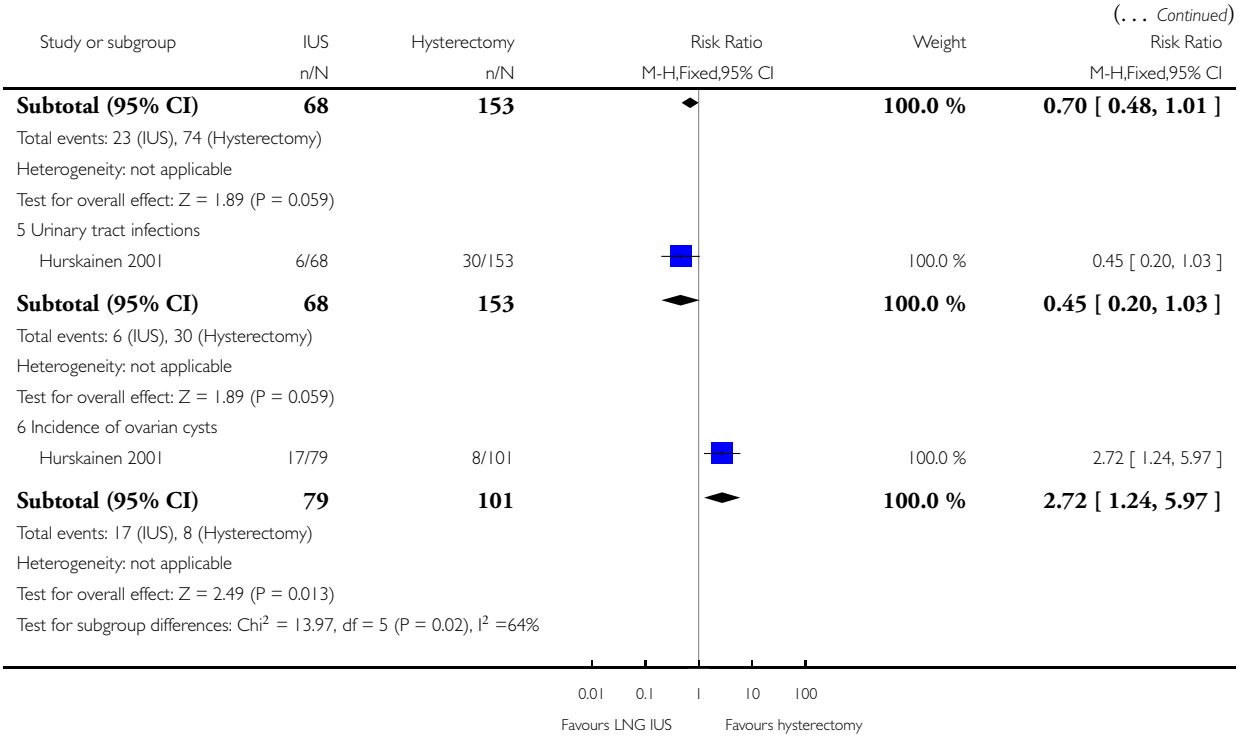

Analysis 4.8. Comparison 4 IUS versus hysterectomy, Outcome 8 Total cost per woman.

Total cost per woman

Study	Details of cost	LNG IUS: Mean cost	LNG IUS: 95% CI	Hyst: Mean cost	Hyst: 95% CI	P value
At 12 months follow-up						
Hurskainen 2001	Total health care costs + product losses/woman	USD 1530	1203 to 1858	USD 4222	3808 to 4636	LNG IUS significantly lower than hysterectomy (figures not reported)
At 5 years follow-up						
Hurskainen 2001	Total cost per participant Discounted total costs (by 3%) (direct and indirect)/woman	USD 2966 USD 2817	2362 to 3679 2222 to 3530	USD 4718 USD 4660	4072 to 5238 4014 to 5180	LNG IUS significantly lower than hysterectomy (figures not reported)

Total cost per woman (*Continued*)

At 10 years follow-up						
Hurskainen 2001	Total cost per participant Discounted total costs per participant	USD 3780 USD 3423	not reported	US$5089 US$4937	not reported	LNG IUS significantly lower than hysterectomy (figures not reported)

APPENDICES

Appendix 1. MDSG search strategy

Keywords CONTAINS "menorrhagia" or "heavy bleeding" or "heavy menstrual bleeding" or "heavy menstrual loss" or "dysfunctional bleeding" or "dysfunctional unterine bleeding" or "dysfunctional uterine bleeding" or "dysfuntional uterine bleeding" or "abnormal uterine bleeding" or "abnormal vaginal bleeding" or "excessive menstrual bleeding" or "excessive menstrual loss" or Title CONTAINS "menorrhagia" or "heavy bleeding" or "heavy menstrual bleeding" or "heavy menstrual loss" or "dysfunctional bleeding" or "dysfunctional unterine bleeding" or "dysfunctional uterine bleeding" or "dysfuntional uterine bleeding" or "abnormal uterine bleeding" or "abnormal vaginal bleeding" or "excessive menstrual bleeding" or "excessive menstrual loss"

AND

Keywords CONTAINS "progestagen" or "Progesterone" or "progestin" or "progestins" or "progestogen" or "progestogens" or "Levonorgestrel" or "levonorgestrel intrauterine system" or "levonorgestrel-releasing intrauterine device" or "levonorgestrel-releasing intrauterine system" or "Levonorgestrel-Therapeutic-Use" or "IUD" or "LNG-IUS" or "Mirena" or "Gestagen" or Title CONTAINS "progestagen" or "Progesterone" or "progestin" or "progestins" or "progestogen" or "progestogens" or "Levonorgestrel" or "levonorgestrel intrauterine system" or "levonorgestrel-releasing intrauterine device" or "levonorgestrel-releasing intrauterine system" or "Levonorgestrel-Therapeutic-Use" or "IUD" or "LNG-IUS" or "Mirena" or "Gestagen"

Appendix 2. CENTRAL search strategy

1 exp Menorrhagia/ (223)
2 Menorrhagia.tw. (300)
3 heavy menstrua$.tw. (50)
4 abnormal uterine bleeding.tw. (79)
5 (dysfunctional adj3 bleeding).tw. (100)
6 hypermenorr$.tw. (13)
7 excessive menstrua$.tw. (15)
8 DUB.tw. (24)
9 heavy period$.tw. (4)
10 ablation.tw. (1762)
11 hysterectom$.tw. (2180)
12 endometrial resection.tw. (70)
13 or/1-12 (4232)
14 progest$.tw. (3658)
15 exp progestins/ or exp progesterone/ (2730)
16 exp Levonorgestrel/ (519)

17 Levonorgestrel.tw. (702)
18 IUS.tw. (79)
19 LNG.tw. (241)
20 mirena.tw. (27)
21 IUD.tw. (335)
22 medicated intrauterine device$.tw. (7)
23 intrauterine contraceptive device$.tw. (75)
24 exp intrauterine devices, medicated/ or exp intrauterine devices, copper/ (273)
25 intrauterine device$.tw. (246)
26 or/14-25 (5746)
27 26 and 13 (293)
28 limit 27 to yr="2005 -Current" (101)

Appendix 3. MEDLINE search strategy

1 exp Menorrhagia/ (3407)
2 Menorrhagia.tw. (2530)
3 heavy menstrua$.tw. (417)
4 abnormal uterine bleeding.tw. (1198)
5 (dysfunctional adj3 bleeding).tw. (860)
6 hypermenorr$.tw. (241)
7 excessive menstrua$.tw. (156)
8 DUB.tw. (516)
9 heavy period$.tw. (85)
10 ablation.tw. (53640)
11 hysterectom$.tw. (25367)
12 endometrial resection.tw. (267)
13 or/1-12 (83621)
14 progest$.tw. (80014)
15 exp progestins/ or exp progesterone/ (70817)
16 exp Levonorgestrel/ (3342)
17 Levonorgestrel.tw. (3374)
18 IUS.tw. (644)
19 LNG.tw. (1072)
20 mirena.tw. (203)
21 IUD.tw. (5984)
22 medicated intrauterine device$.tw. (25)
23 intrauterine contraceptive device$.tw. (1525)
24 exp intrauterine devices, medicated/ or exp intrauterine devices, copper/ (2653)
25 intrauterine device$.tw. (3803)
26 or/14-25 (118412)
27 26 and 13 (3187)
28 randomized controlled trial.pt. (367251)
29 controlled clinical trial.pt. (87702)
30 randomized.ab. (282868)
31 randomised.ab. (56195)
32 placebo.tw. (155352)
33 clinical trials as topic.sh. (169895)
34 randomly.ab. (202864)
35 trial.ti. (121620)
36 (crossover or cross-over or cross over).tw. (59114)
37 or/28-36 (916821)

38 exp animals/ not humans.sh. (3908595)
39 37 not 38 (846616)
40 27 and 39 (452)
41 (2005$ or 2006$ or 2007$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$).ed. (7505743)
42 40 and 41 (190)

Appendix 4. EMBASE search strategy

1 exp Menorrhagia/ (6207)
2 Menorrhagia.tw. (3405)
3 heavy menstrua$.tw. (589)
4 abnormal uterine bleeding.tw. (1637)
5 (dysfunctional adj3 bleeding).tw. (1051)
6 hypermenorr$.tw. (275)
7 excessive menstrua$.tw. (173)
8 DUB.tw. (609)
9 heavy period$.tw. (103)
10 ablation.tw. (69209)
11 hysterectom$.tw. (32462)
12 endometrial resection.tw. (387)
13 or/1-12 (108307)
14 progest$.tw. (83986)
15 Levonorgestrel.tw. (3887)
16 IUS.tw. (1016)
17 LNG.tw. (1462)
18 mirena.tw. (1057)
19 IUD.tw. (4505)
20 medicated intrauterine device$.tw. (26)
21 intrauterine contraceptive device$.tw. (1475)
22 intrauterine device$.tw. (4127)
23 exp gestagen/ or exp levonorgestrel/ or exp progesterone/ (133604)
24 exp intrauterine contraceptive device/ or exp copper intrauterine device/ (12958)
25 or/14-24 (171865)
26 13 and 25 (5051)
27 Clinical Trial/ (877996)
28 Randomized Controlled Trial/ (344075)
29 exp randomization/ (61535)
30 Single Blind Procedure/ (17488)
31 Double Blind Procedure/ (115062)
32 Crossover Procedure/ (37150)
33 Placebo/ (219517)
34 Randomi?ed controlled trial$.tw. (87671)
35 Rct.tw. (11542)
36 random allocation.tw. (1242)
37 randomly allocated.tw. (18835)
38 allocated randomly.tw. (1885)
39 (allocated adj2 random).tw. (720)
40 Single blind$.tw. (13377)
41 Double blind$.tw. (136734)
42 ((treble or triple) adj blind$).tw. (315)
43 placebo$.tw. (189290)
44 prospective study/ (235630)

45 or/27-44 (1334059)
46 case study/ (20085)
47 case report.tw. (244994)
48 abstract report/ or letter/ (871309)
49 or/46-48 (1131248)
50 45 not 49 (1297572)
51 26 and 50 (1201)
52 (2010$ or 2011$ or 2012$ or 2013$).em. (3840353)
53 51 and 52 (258)

Appendix 5. CINAHL search strategy

#	Search strategy CINAHL AL159 Query 19.06.13	Results
S39	S23 AND S37	56
S38	S23 AND S37	81
S37	S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36	Display
S36	TX allocat* random*	Display
S35	(MH "Quantitative Studies")	Display
S34	(MH "Placebos")	Display
S33	TX placebo*	Display
S32	TX random* allocat*	Display
S31	(MH "Random Assignment")	Display
S30	TX randomi* control* trial*	Display
S29	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	Display
S28	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	Display
S27	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	Display
S26	TX clinic* n1 trial*	Display
S25	PT Clinical trial	Display

(*Continued*)

S24	(MH "Clinical Trials+")	Display
S23	S12 AND S22	303
S22	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21	5,084
S21	TX intrauterine contraceptive device	86
S20	(MM "Intrauterine Devices") OR "intrauterine devices"	1,462
S19	TX medicated intrauterine device*	2
S18	TX IUD	433
S17	TX mirena	70
S16	TX LNG	102
S15	TX Levonorgestrel	992
S14	(MM "Levonorgestrel") OR "Levonorgestrel"	978
S13	(MH "Progestational Hormones+")	2,960
S12	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11	16,340
S11	TX endometrial resection	59
S10	TX hysterectom*	4,602
S9	TX ablation	11,084
S8	TX heavy period*	117
S7	TX excessive menstrua*	27
S6	TX hypermenorr*	10
S5	TX (dysfunctional uterine bleeding)	108
S4	TX abnormal uterine bleeding	203
S3	TX heavy menstrua*	177
S2	TX Menorrhagia	819

(*Continued*)

S1	(MM "Menorrhagia")	451

Appendix 6. PsycINFO search strategy

1 exp Menstrual Disorders/ (973)
2 Menorrhagia.tw. (66)
3 heavy menstrua$.tw. (10)
4 abnormal uterine bleeding.tw. (7)
5 (dysfunctional adj3 bleeding).tw. (22)
6 hypermenorr$.tw. (2)
7 excessive menstrua$.tw. (5)
8 DUB.tw. (83)
9 heavy period$.tw. (8)
10 ablation.tw. (2963)
11 hysterectom$.tw. (658)
12 endometrial resection.tw. (4)
13 or/1-12 (4716)
14 progest$.tw. (3674)
15 exp Progestational Hormones/ (1935)
16 exp Intrauterine Devices/ (76)
17 Levonorgestrel.tw. (48)
18 IUS.tw. (67)
19 LNG.tw. (24)
20 mirena.tw. (8)
21 IUD.tw. (115)
22 intrauterine contraceptive device$.tw. (11)
23 intrauterine device$.tw. (150)
24 or/14-23 (4080)
25 13 and 24 (110)
26 random.tw. (37959)
27 control.tw. (295425)
28 double-blind.tw. (16957)
29 clinical trials/ (6785)
30 placebo/ (3474)
31 exp Treatment/ (548240)
32 or/26-31 (834863)
33 25 and 32 (62)
34 limit 33 to yr="2005 -Current" (21)

WHAT'S NEW

Last assessed as up-to-date: 20 January 2015.

Date	Event	Description
20 January 2015	New search has been performed	Review updated in 2015. Twelve new trials added to the review (de Souza 2010; Ergun 2012; Gupta 2013; Kaunitz 2010; Kilic 2009; Malak 2006; Ozdegirmenci 2011; Sayed 2011; Sesti 2012; Shabaan 2011; Shaw 2007; Tam 2006).
20 January 2015	New citation required and conclusions have changed	Twelve new trials added to the review. Conclusions changed.

HISTORY

Protocol first published: Issue 3, 1996

Review first published: Issue 2, 2000

Date	Event	Description
23 August 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Prior to the 2015 update:

Inez Cooke registered the title, reviewed potential studies for eligibility, assessed the quality of the included studies, performed data extraction, submitted the protocol in 1996 and prepared a draft of the review. For the 2003 update of the review, Inez reviewed potential studies for eligibility, assessed quality, performed data extraction, edited and commented on the text of the final review and wrote the discussion section.

Margaret Rees reviewed potential studies for eligibility, assessed the quality of the included studies, performed data extraction and reviewed and edited the completed draft of the review for the 1999 publication.

Anne Lethaby conducted additional searches in 1999, reviewed potential studies for eligibility, assessed the quality of the included studies, performed data extraction, entered data and prepared the draft of the final review with the inclusion of additional studies. For the 2003 update of the review, Anne performed additional searches, reviewed potential studies for eligibility, assessed the quality of the included studies, performed data extraction, entered data and modified the review to incorporate the results of the additional studies. A final search was performed in July 2005 just prior to publication of the update.

2015 update:

Munawar Hassain reviewed potential studies for eligibility and performed data extraction of the included studies. He also wrote the background section and commented on the draft text of the final review.

Josephine Rishworth assessed the quality of the included studies.

Anne Lethaby reviewed potential studies for eligibility, assessed the quality of the included studies, performed data extraction, entered data, modified the review to incorporate the results of the additional studies and prepared the draft of the final review.

Margaret Rees assessed the quality of the included studies and commented on the final draft.

DECLARATIONS OF INTEREST

There is no conflict of interest to declare.

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynaecology, National Womens Hospital and University of Auckland, Auckland, New Zealand.

External sources

- NHS Executive Anglia and Oxford Region R & D Programme, UK.
- Health Research Council, Auckland, New Zealand.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The 2015 update amended the list of included outcomes (from the protocol) as follows:

The following outcomes specified in the protocol were deleted: Duration of MBL in days, number of sanitary pads per cycle, acceptability of treatment and mortality. Duration of menstrual blood loss and number of sanitary pads per cycle were excluded as there is no evidence of a correlation between the extent of blood loss and these outcomes (Chimbira 1980). The outcome, acceptability of treatment, was considered to be too similar to satisfaction with treatment. Mortality was considered a rare event that was unlikely to be measured in studies.

One study that had been included prior to the 2015 update (Lahteenmaki 1998) was excluded because it no longer measured any of the amended outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

*Intrauterine Devices, Medicated [adverse effects]; Endometrium [surgery]; Hysterectomy; Levonorgestrel [administration & dosage; *therapeutic use]; Medroxyprogesterone [administration & dosage; therapeutic use]; Menorrhagia [*drug therapy; surgery]; Norethindrone [administration & dosage; *therapeutic use]; Progesterone [administration & dosage; *therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans