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

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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, 80mls blood loss per menstrual cycle but women may complain of excessive bleeding when their blood loss is less than 80ml. Hysterectomy is often used to treat women with this complaint but medical therapy may be a successful alternative.

The intrauterine coil device was originally developed as a contraceptive but the addition of uterine relaxing hormones, or progestogens, to these devices resulted in a large reduction in menstrual blood loss. Case studies of 2 types of progesterone/progestogen releasing systems, Progestasert and Mirena, report reductions of up to 90% and dysmenorrhoea
may be improved. Insertion, however, may be regarded as invasive by some women affecting its acceptability as a treatment and frequent intermenstrual bleeding and spotting is likely during the first few months.

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

Search strategy
All studies which might describe randomised controlled trials of progesterone/progestagen-releasing intrauterine devices for the treatment of heavy menstrual bleeding were obtained by electronic searches of the MEDLINE 1966-1999, EMBASE 1980-1999 databases and the Cochrane Library. 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progestogen releasing intrauterine devices and experts in the field were contacted for information on published and unpublished trials.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/progestogen-releasing intrauterine devices versus no treatment, placebo, or other medical or surgical therapy for heavy menstrual bleeding within either the primary care, family planning or specialist clinic setting 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 three reviewers and five trials met the criteria for inclusion in the review. The reviewers extracted the data independently and data were pooled where appropriate. Odds ratios for dichtomous outcomes and weighted mean differences for continuous outcomes were estimated from the data. The primary outcome was reduction in menstrual blood loss but incidence of side effects, changes in quality of life and satisfaction and acceptability measures were also assessed.

Main results
Progesterone/progestogen-releasing intrauterine systems have not been compared to placebo or no treatment.

Progestasert has been compared to a number of different medical therapies in one small study but no conclusions can be made about effectiveness. The levonorgestrel-releasing intrauterine device (LNG IUS) has been compared to oral cyclical norethisterone (NET) administered on days 5-26 in one trial and was significantly more effective although there was a large reduction from baseline in both groups and these differences were not perceived by the women undergoing the treatment. Some side effects were more common in the LNG IUS group but a significantly greater proportion of women in this group were satisfied and willing to continue with their treatment. In one trial of women awaiting hysterectomy where the LNG IUS was compared with a control group taking their existing medical therapy, a higher proportion of the women in the former group cancelled their planned surgery after 6 months of treatment.

The levonorgestrel-releasing intrauterine device has been compared to a surgical procedure (transcervical resection of the endometrium (TCRE)) in two trials. There was a significantly greater mean reduction in menstrual bleeding in those undergoing TCRE, a lower score on the pictorial blood loss chart and higher rates of amenorrhoea but this was not perceived by the women when the difference in rates of bleeding or rates of satisfaction with treatment was assessed. There was no conclusive evidence of changes in quality of life between groups but women with the LNG IUS had a greater incidence of progestogenic side effects and intermenstrual bleeding.

Authors' conclusions

The levonorgestrel-releasing intrauterine device (LNG IUS) is more effective than cyclical norethisterone (21 days) as a treatment for heavy menstrual bleeding. Women with an LNG IUS are more satisfied and willing to continue with treatment but experience more side effects such as intermenstrual bleeding and breast tenderness.

The LNG IUS results in a smaller mean reduction in menstrual blood loss than transcervical resection of the endometrium (TCRE) and women are not as likely to become amenorrhoeic but there is no difference in the rate of satisfaction with treatment. Women with an LNG IUS experience more progestogenic side effects compared to women having TCRE for treatment of their heavy menstrual bleeding but there is no difference in their perceived quality of life.

There are no data available from randomised controlled trials comparing progesterone-releasing intrauterine systems to either placebo or other commonly used medical therapies for heavy menstrual bleeding.

SYNOPSIS

Progesterone/progestogen-releasing intrauterine systems have been assessed for efficacy, acceptability and safety for the treatment of heavy menstrual bleeding. The most commonly studied, the levonorgestrel-releasing intrauterine system (LNG IUS), is more effective than oral norethisterone taken over 21 days of the cycle and women are more satisfied and willing to continue with treatment but side effects are more frequent. Although the LNG IUS results in a smaller reduction in menstrual blood loss than a surgical procedure, transcervical resection of the endometrium (TCRE) and women encounter more side effects, there are no differences in the women's rate of satisfaction or quality of life. There have been no other randomised comparisons of the LNG IUS with other medical or surgical treatments.

BACKGROUND

Heavy menstrual bleeding (HMB) is an important cause of ill health in women. One in 20 women aged 30-49 in the UK consult their General Practitioner (GP) each year with heavy menstrual bleeding (Peto 1993) and it accounts for 12% of all gynaecology referrals (Bradlow 1992). A comparable prevalence rate and referral rate is likely in other Western countries (NHC NZ 1998).

Menorrhagia or heavy menstrual bleeding (HMB) is clinically defined as greater than, or equal to 80mls blood loss per menstrual cycle (Cole 1971; Hallberg 1966) but it is the woman's perception of her own menstrual loss which is the key determinant in her referral and indeed subsequent treatment. Eighty per cent of women treated for menorrhagia have no anatomical pathology and over one third of the women undergoing hysterectomies for heavy menstrual bleeding have anatomically normal uteri removed (Clarke 1995; Gath 1982). Hence 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).

The intrauterine coil device (IUCD) has primarily been a method of contraception. Progesterone/progestogen-releasing intrauterine systems (PPRIUS) were initially introduced in an effort to reduce IUCD expulsion by the addition of 'uterine-relaxing hormones' (Odlind 1996). Subsequently, prolonged use of both the Progestasert (the first hormonally impregnated device releasing 65mcg

of progesterone per day) and Mirena (a device releasing 20ug of levonorgestrel per day) intrauterine systems was associated with a profound reduction in menstrual blood loss in women using the IUCD for contraception. Twenty per cent of the women using the levonorgestrel-releasing intrauterine system were amenorrhoeic after one year's use (Andersson 1994) whilst still continuing to ovulate.

Both the Progestasert and levonorgestrel-releasing intrauterine system (Mirena) have been reported to reduce heavy menstrual bleeding by up to 90% in case studies (Berqvist 1983; Andersson 1994). However, Progestasert requires re-insertion every 18 months. The levonorgestrel-releasing intrauterine system, which has to be replaced every 5 years, has been compared favourably to other medical treatments for heavy cyclical blood loss (Milsom 1991). Dysmenorrhoea appears to occur less frequently and it has been suggested that the incidence of pelvic inflammatory disease may be reduced in users, particularly those under the age of 25 years by thickening the utero-cervical mucus (Andersson 1994). However, the device is broader than copper bearing IUDs and insertion may require local anaesthesia and dilation of the cervical canal in nulliparous or peri-menopausal women. Insertion is an invasive procedure which may not be acceptable to some women. A major 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 preparation should its use be discontinued earlier than the five year lifespan for which it is licensed as an effective contraceptive, because of pelvic pain or dissatisfaction with the progestogenic side effects.

OBJECTIVES

To determine the effectiveness of the progesterone/progestogen-releasing intrauterine devices in achieving a reduction in menstrual flow.

We wished to test the following hypotheses:

1. Progesterone/progestogen-releasing intrauterine systems are more effective than placebo in reducing menstrual flow.

2. Progesterone/progestogen-releasing intrauterine systems are more effective than any other therapy (either medical or surgical) in reducing menstrual flow.

3. Progesterone/progestogen-releasing intrauterine systems lead to an improved quality of life for women with heavy menstrual bleeding when compared with no treatment, placebo or other therapy.

4. Progesterone/progestogen-releasing systems result in fewer side effects than other treatments for the reduction of heavy menstrual bleeding.

5. Progesterone/progestogen-releasing intrauterine systems are more acceptable to women than other treatments for the reduction of heavy menstrual bleeding.

6. Progesterone/progestogen-releasing intrauterine systems are a cost-effective method of treating heavy menstrual bleeding.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomised controlled trials of the progesterone/progestagen-releasing intrauterine devices versus no treatment, placebo, or other medical or surgical therapies when used to reduce heavy menstrual bleeding.

Types of participants

Inclusion criteria:
Women of reproductive years with regular heavy periods measured either objectively (by the alkaline haematin method) or subjectively (patient perception)

Exclusion criteria:
Postmenopausal bleeding (>1 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

Source of recruitment:
Primary care, family planning or specialist clinics

Types of intervention

Progesterone/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

For the progesterone/progestogen-releasing intrauterine devices versus no treatment, placebo or any other treatment (medical or surgical), each of the following outcomes will be recorded where available. Of these the primary outcome of interest is the objective reduction in cyclical blood loss.

Objective assessment of menstrual blood loss (measured by the alkaline haematin method)
- Mean blood loss during treatment (mls)
- Mean reduction in blood loss from baseline to treatment (mls)

Menstrual blood loss - measured by Pictorial Bleeding Assessment Chart score (PBAC)
Subjective assessment of menstrual blood loss - either better or the same/worse (participant's perception)

Indirect measures of menstrual blood loss
- Duration of loss (days)
- Number of sanitary pads/cycle

Quality of life: Participant's perceived change in quality of life provided this has been recorded in a reproducible and validated format (for example SF 12 or SF 36) or subjectively by participant questionnaires

Side effects:
- Proportion of women with side effects of any type
- Pelvic inflammatory events
- Ectopic pregnancy events
- Menstrual pelvic pain (dysmenorrhoea)
- Menstrual irregularity or intermenstrual bleeding
- Expulsion of IUCD
- Progestogenic side effects (such as acne, weight gain, bloating, breast tenderness)

Withdrawal from treatment because of adverse events

Acceptability of treatment to participants

Satisfaction with treatment

Resource cost

Mortality

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: search strategy

All studies which might describe randomised controlled trials of progesterone/progestagen-releasing intrauterine devices for the treatment of heavy menstrual bleeding were obtained using the search strategy developed by the Cochrane Menstrual Disorders and Subfertility Group (see Review Group details for more information) with the addition of the terms levonorgestrel, levonorgestrel-releasing intrauterine devices, intrauterine-device-medicated and other comparable terms. The electronic databases MEDLINE (1966-1999), EmBASE (1980-1999) and Current Contents (1995-1999) were searched. The Trials Search Coordinator also performed regular searches of the Trial Register of the Review Group.

Other databases listing ongoing or recently completed trials, such as CentreWatch and NRR, were also searched. Handsearching of relevant journals was perfomed and citation lists of included trials, conference abstracts and relevant review articles were also searched.

Schering produces progesterone/progestagen-releasing intrauterine devices. They provided a list of ten published papers on the use of these intrauterine devices and their effects on heavy menstrual bleeding, one of which was a randomised controlled trial.

Letters were also sent to experts within the field for reference lists and a list of potential trials was drawn up.

METHODS OF THE REVIEW

The review has been undertaken by three reviewers (MR, AL and IC). Both IC and MR are content experts and AL has methodological expertise. The initial search strategy produced 221 abstracts from MEDLINE and 835 abstracts from EMBASE potentially relevant to the review. These were screened by IC to exclude those studies which were clearly ineligible. Following this search, the full texts of 10 studies were retrieved. AL also independently performed follow up searches and retrieved additional potential studies.

Studies were reviewed independently by MR and IC and AL to assess whether the studies met the inclusion criteria, with disagreements resolved by discussion. The reviewers were not blinded to the details of authors or institutions of these studies.

The quality of all studies which were deemed eligible for the review were assessed independently by all of the reviewers with discrepancies resolved by discussion. The quality of allocation concealment was graded as either adequate (A), unclear (B) or inadequate (C), following the detailed descriptions of these categories provided by the Cochrane Menstrual Disorders and Subfertility Review Group. It was intended to use this grading in the investigation of any heterogeneity (variations) between trials and in the sensitivity analyses; however, there were never more than two trials within each meta-analysis so these analyses were not performed. These quality gradings and analyses will however become increasingly important as the number of trials within this clinical area increases. Other aspects of study quality including the extent of blinding, baseline comparability, power calculations, extent of losses to follow-up, and whether an 'intention to treat' analysis was undertaken were assessed using the standard checklist developed by the Menstrual Disorders and Subfertility Review Group. This information is presented in the table describing the included studies.

The results sections and extra unpublished information obtained for the included studies were assessed by (MR, AL and IC) for data extraction using proformas designed by the Review Group. Discrepancies were resolved by discussion. For each included trial, information was collected regarding the location of the study, methods of the study, description of the participants and interventions and data relating to the outcomes specified in the selection criteria section above.

Statistical analyses were performed according to the statistical guidelines for the reviewer in the Cochrane Menstrual Disorders and Subfertility Review Group. In the meta-analysis, the Peto modified Odds Ratio measure of effect was used for each dichotomous outcome and the summary statistics calculated using both the Fixed Effect and a Random Effects model. Sensitivity analyses were unhelpful because of the small number of trials included with the review.

Difficulties were encountered with the reporting of continuous outcomes. Meta-analysis with RevMan software offers a weighted mean difference (WMD) option to combine outcomes and requires data to be presented as absolute values of means with their standard deviations. For many outcomes, particularly mean blood loss, the data were skewed and the medians and ranges reported in the published papers. These data have been presented in the Other Data section of the review since it was not appropriate to pool them to produce an overall estimate of effect.

In many studies of progesterone/progestogen-releasing intrauterine systems retrieved using the search strategy above, whilst menstrual blood loss was a measured outcome, the criteria for inclusion within the trial was a need for contraception or relief of climacteric symptoms but heavy menstrual bleeding was not the presenting complaint. These trials did not meet the inclusion criteria of this review but the references have been included in the additional reference section for clarity.

There were only a small number of randomised controlled trials of progesterone/progestogen-releasing intrauterine systems.

DESCRIPTION OF STUDIES

EXCLUDED TRIALS

A number of trials were case series and did not fulfil the inclusion criteria for randomisation. One randomised trial (Janssen 1999) was excluded because a proportion of participants (22%) did not have heavy menstrual bleeding.

INCLUDED TRIALS

Studies

Five randomised controlled trials met the criteria for inclusion.

Interventions

Of the five randomised controlled trials that met the inclusion criteria for this review, one trial compared the levonorgestrel-releasing intrauterine system (LNG IUS) with norethisterone (long cycle) (Irvine 1998), two trials compared LNG IUS with transcervical resection of the endometrium (Crosignani 1997; Kittelsen 1998), one trial compared the LNG IUS with a control group that were given a variety of medical treatments (Lahteenmaki 1998) and one trial compared the Progestasert coil with the combined oral contraceptive pill, danazol and norethisterone (short course) (Cameron 1987). No trials were identified that compared intrauterine devices with placebo or no treatment.

Crosignani 1997, Irvine 1998, Kittelsen 1998 and Lahteenmaki 1998 all used the levonorgestrel-releasing intrauterine system which releases 20ug/day of levonorgestrel. The device was inserted into the uterine cavity within 7 days of the last menstrual period. Cameron 1987 used the intrauterine system, Progestasert, which releases 65mcg of progesterone daily and results from this study were reported separately. 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.

Participants

One trial (Irvine 1998) required that the study participants measure their menstrual blood loss over one pre-treatment cycle and they were randomised only after their blood loss was confirmed as greater than 80mls per cycle, as measured by the alkaline haematin method. Two trials (Crosignani 1997; Kittelsen 1998) required that participants have scores of 100 or higher on a pictorial blood-loss assessment chart (Higham 1990). A monthly score of 100 or more on this chart is significantly associated with heavy menstrual bleeding of more than 80mls per cycle, as measured by the alkaline haematin method (Janssen 1995). One trial enrolled women who were on hospital waiting lists for hysterectomy for excessive uterine bleeding (Lahteenmaki 1998). The other trial, evaluating Progestasert (Cameron 1987), required that women have a MBL >50mls per cycle. The other inclusion and exclusion criteria are detailed in the Table of Included Studies.

The trials included in the review represent results for a total of 260 participants.

Outcomes

The two trials comparing LNG IUS with TCRE assessed efficacy of treatment by scores on the pictorial blood loss assessment chart (Crosignani 1997; Kittelsen 1998). The proportion of women who experienced amenorrhoea was also noted by 3 trials, one after 3 months of treatment and two after 12 months (Irvine 1998; Crosignani 1997; Kittelsen 1998).

Two studies assessed menstrual blood loss after treatment objectively by the alkaline haematin method but the data were too skewed to pool for a combined measure of effect and the results are included in the Other Data section of the review (Irvine 1998; Cameron 1987). Number of days of bleeding after treatment were also recorded by 2 studies and reported in the Other Data section of the review (Cameron 1987; Lahteenmaki 1998).

Quality of life after treatment was assessed in a number of different ways. The Short Form 36 Health Survey questionnaire, with 8 items, was administered 12 months after treatment by Crosignani 1997. Lahteenmaki 1998 required that participants mark a visual analogue scale (VAS) on 5 items 6 months after treatment indicating the effects of their uterine bleeding or menstrual pain, without distinguishing between these two. Irvine 1998 measured the proportion of participants who perceived that their menstruation interfered with their normal life after 3 months of treatment. Satisfaction with treatment was recorded by 2 studies (Irvine 1998; Crosignani 1997) and the proportion of women who found their treatment acceptable, as indicated by their willingness to continue treatment, was recorded by one study (Irvine 1998). The main

outcome for another study was the willingness to continue with current treatment instead of the scheduled hysterectomy after 6 months of randomised treatment (Lahteenmaki 1998).

One trial recorded the proportion of women who suffered specific adverse events (Irvine 1998), one trial recorded the proportion of women who suffered any side effects resulting from treatment (Crosignani 1997) and two trials recorded the proportion who withdrew from the trial as a result of adverse events relating to the treatment (Irvine 1998; Kittelsen 1998) (this was only recorded for the Irvine study because the other trial was a comparison of LNG IUS with TCRE where withdrawal from one arm was not possible and so could not be compared).

Some of the outcomes from 3 of the studies could be pooled in the meta-analysis. Other outcomes could not be pooled because the data were heavily skewed and individual participant data were not available for transformation.

The duration of treatment before assessment in the 3 trials that compared the IUS with medical treatments was 2, 3 and 6 months. Follow up for the remaining 2 trials comparing LNG IUS with TCRE was 6 and 12 months for one study and a mean of 12 months for the other. This latter trial (Kittelsen 1998) has been extended for a total of 36 months but the data are not yet available. From the case series studies, it is known that menstrual irregularity may be problematic in the first months after insertion of the LNG IUS; hence assessment of this method after two or three months may give a misleadingly poor outcome.

METHODOLOGICAL QUALITY

Allocation to treatment group or control was randomised in all trials but in one trial the method was not described. Randomisation was computer generated in two trials and concealment of allocation ensured by using consecutively numbered opaque envelopes in four trials (Irvine 1998; Crosignani 1997; Lahteenmaki 1998; Kittelsen 1998). Three of the trials had performed power calculations for sample size and analysis was by intention to treat but in one study, the trialists were unable to achieve their target of participant accrual of 95% power. It is unlikely that participant blinding was used in any of the trials because of practical difficulties, for example, surgery in the control group. There is no indication given of blinding of the assessors.

Four of the five trials were single centre studies and 1 trial was carried out in 3 centres.

Withdrawals after randomisation varied from 1.4% to 18%. In one trial, one out of 70 participants was lost to follow up, in another trial 3/56 women withdrew after randomisation and in another 8/44 withdrew mostly because of adverse events (2/22 in the LNG IUS group and 6/22 in the norethisterone group); in all of these trials, however, analysis was by intention to treat (although some of the outcomes such as adverse events were analysed per protocol). One trial did not report any withdrawals and the other reported that 12% (7/60) discontinued their treatment (6/30 in the LNG IUS group and 1/30 in the TCRE group). It must be noted that withdrawal from "treatment" in a surgical arm of a trial in not really possible unless that is accomplished before the surgery has taken place. However, a participant may at any stage withdraw from treatment (either discontinue medication or request the removal of the IUD) at any stage during the other arms of trials included in this review.

Women's subjective assessments and attitudes towards continuation of treatment and effect of menstrual condition on quality of life measures are likely to have been affected by the trial design in one study. In the Lahteenmaki 1998 study, women were randomised to either a "new" treatment, the LNG IUS, or to a group continuing with their existing medical treatment. The lack of blinding in this study together with the treatment options, one of which is new, is likely to have affected womens' attitudes towards the treatment and its effect on their heavy menstrual bleeding.

Due to the small number of trials at this stage, sensitivity analyses based on trial quality were not possible.

RESULTS

PROGESTOGEN-RELEASING INTRAUTERINE SYSTEM VERSUS PLACEBO OR NO TREATMENT

No trial provided a comparison of progestagen-releasing intrauterine devices to either a placebo or no treatment group.

PROGESTOGEN-RELEASING INTRAUTERINE SYSTEM VERSUS ANY OTHER MEDICAL THERAPY

Three trials were identified which compared the IUS with medical treatment. One trial (Irvine 1998) compared the levonorgestrel-releasing intrauterine device with oral norethisterone given during days 5 to 26 of the menstrual cycle. Another trial (Cameron 1987) compared the Progestasert IUS with mefenamic acid, danazol and norethisterone given during the luteal phase (second half) of the cycle (numbers in each group were very small). The third trial (Lahteenmaki 1998), of women awaiting hysterectomy for excessive bleeding, compared the levonorgestrel-releasing IUS with a group which continued with their current medical treatment. No details of type of medical treatment were provided in the published paper. It is recognised that all medical treatment for heavy menstrual bleeding does not necessarily have similar effect but in this trial, results appear to be reported with all medical treatment combined in the control group. The results of most of the outcomes for these trials were included in the Other Data section of the review either because the data were heavily skewed or because the treatment groups were not comparable at baseline so statistical tests comparing after treatment values were not valid.

The Progestasert device and the LNG IUS were both effective in reducing menstrual blood loss. The Progestasert device did not appear to be more effective than either mefenamic acid or danazol in one small trial although it may have been more effective than oral norethisterone given during the luteal phase (Cameron 1987); however, the groups in this study were very small and menstrual blood loss was not comparable at baseline so no statistical tests were performed. The LNG IUS was more effective than oral norethisterone (NET) given during days 5 to 26 in the menstrual cycle in one trial with a power calculation and intention to treat analysis after three months treatment although there was a big reduction in both groups from baseline (median 6mls, range 0-248 mls vs median 20mls, range 4-137 mls) . The median reduction from baseline, however, was not significantly different between groups. A greater proportion of women were amenorrhoeic after 3 months of treatment in the LNG IUS group when compared with the NET group (32% vs 0%). There was no indication that number of days of menstrual bleeding differed between treatment groups in two trials. Some side effects (intermenstrual bleeding and breast tenderness) were significantly more common in the LNG IUS group when compared with the NET group. Rates of satisfaction with treatment (liking the treatment "well" or "very well") did not differ between groups. However, a significantly greater proportion of women in the LNG IUS group were willing to continue with their treatment when compared with the NET group (77% vs 22%).

In the trial where the LNG IUS was compared with a control group taking medical therapy, all quality of life scores were significantly better in the former group. In addition, women in the LNG group were significantly more likely to cancel their scheduled hysterectomy after 6 months of treatment when compared with women continuing on their existing medical treatment.

PROGESTOGEN-RELEASING INTRAUTERINE SYSTEM VERSUS ANY SURGICAL TREATMENT

Two trials (Crosignani 1997; Kittelsen 1998) compared the levonorgestrel-releasing intrauterine device to transcervical resection of the endometrium. A significantly greater mean reduction of blood loss (WMD 27.0 (16.8,37.6)) and a significantly lower mean pictorial blood chart score (WMD 18.5 (2.4, 34.7) was found in those women who received transcervical endometrial resection compared to those with an levonorgestrel-releasing intrauterine device in situ. This was not mirrored in a significant difference in mean blood loss between the two groups (WMD 12.2 (-1.9, 26.3)). In addition, a significantly greater proportion of women who had TCRE were amenorrhoeic than women having the LNG IUS (46.2% vs 26.6%) at 12 months follow up. Other indirect measurements of blood loss such as duration of loss or sanitary pad usage were not recorded. There was also no significant difference in rates of satisfaction with treatment (IUS: 85%; TCRE: 94%) between groups.

There was no significant difference in the incidence of dysmenorrhea at 12 months follow-up (RR 2.1 (0.2, 21.7)) but overall there were a significantly higher incidence of side effects recorded in the LNG IUS group (55.9% vs 25.7%). However, no differences were demonstrated in the eight different dimensions in the Short Form 36 questionnaire at 12 months follow up in one trial (Crosignani 1997). In this Italian study, the distribution of scores were generally similar in the 2 study groups and they were also similar to normative data for the general Italian female population (results given in the Other Data section).

In one trial, the levonorgestrel-releasing intrauterine device was partially expelled in 2 out of 34 (5.9%) cases who refused further treatment and intermenstrual spotting was recorded in 12 out of 34 (35.2%) cases. In the other trial, 6 out of the 30 randomised LNG IUS participants discontinued treatment during the follow up period, 3 because of irregular bleeding and continuous spotting, 2 because of pain and the other because of skin problems.

DISCUSSION

With the discovery that the addition of a progestogen to an inert contraceptive device improved its contraceptive action, Progestasert was the first hormonally impregnated device to be marketed. In a non-randomised study, menstrual blood loss was reduced between 18 and 71% below control levels with long term use (Larsson 1983) and in one small randomised study, menstrual blood loss was reduced by 22.5% (Cameron 1987). The levonorgestrel-releasing intrauterine system (Mirena) has been developed as a contraceptive device over the last decade but was licensed for use in the UK in 1995 and in 12 other countries by 1998. Despite it being such a new intervention in gynaecology, it has very rapidly become a much used treatment for heavy menstrual bleeding. However, this rapid introduction of a new therapy for menorrhagia has been based mainly on evidence from case series rather than evaluation of the levonorgestrel-releasing intrauterine system in randomised controlled trials. Nevertheless, the randomised controlled trials described here do highlight the levonorgestrel-releasing intrauterine system as a useful treatment for heavy menstrual bleeding with the additional advantage of being a contraceptive which is effective for 5 years with fertility quickly restored after its removal. However, the small number of trials should also alert us to the possible publication bias towards those trials showing only positive results since no unpublished trials were identified. Some caution must be exercised in the interpretation of results in the meta-analysis in this review, since, in most cases, these are based on only one small trial.

MENSTRUAL BLOOD LOSS: objective measurements

On the available evidence, the levonorgestrel-releasing intrauterine system significantly reduces menstrual blood loss from baseline and is more effective than oral progestogens taken for 21 days each cycle. However, this is based on a small number of women from one trial only and is measured after only 3 months of treatment.

MENSTRUAL BLOOD LOSS: subjective and indirect measurements

Blood loss measurements, as assessed by pictorial blood loss chart scores, are significantly lower in women who have TCRE compared to women who have the LNG IUS. Other indirect measurements of menstrual blood loss such as number of sanitary pads used and duration of loss have either not been reported or show no difference between groups and are now known to correlate poorly with the actual menstrual blood loss (Chimbira 1980).

Rates of amenorrhoea are significantly higher at 3 months in the LNG IUS group compared with the group taking 21 days of oral progestogen but significantly lower at 12 months when compared with the group having TCRE. This finding is in agreement with the results relating to efficacy, measured objectively in the same trials. The former comparison, however, was assessed after 3 months of treatment which is unlikely to be long enough to adequately assess ongoing or long term effectiveness.

Most of the studies included in this review have specified that the participants must have excessive blood loss during their menstrual period (requirement that blood loss measured objectively is >80mls/cycle or a pictorial blood loss chart score >100). The concern which is important to the clinician and woman is whether this decrease in menstrual blood loss when the levonorgestrel-releasing intrauterine system is inserted is only seen in those women with >80mls/cycle of blood loss or whether the same reduction in blood loss will occur in the 50% of women who, whilst complaining of heavy menstrual bleeding, would have cyclical menstrual losses of <80mls/cycle. It is reassuring that menstrual blood loss was less than 80mls/cycle in 20 out of 22 women with a levonorgestrel-releasing intrauterine system in situ (Irvine 1998).

QUALITY OF LIFE MEASUREMENTS.

In two trials which assessed quality of life after treatment, there are no significant differences shown between the LNG IUS and the other treatment (Irvine 1998; Crosignani 1997). However, both trials confirm that the number of participants recruited was not adequate to show changes in satisfaction or quality of life since the statistical power was calculated on the basis of changes in menstrual blood loss only. In another trial where the LNG IUS was compared with a control group continuing with their medical therapy, the women with the LNG IUS scored significantly higher on a number of different items of quality of life (general well being, work performance, physical activity, sex life and leisure time activity) (Lahteenmaki 1998), but the nature of the interventions offered may have affected womens' attitudes toward improvement in their well being.

ADVERSE EVENTS

The levonorgestrel-releasing intrauterine system is licensed as effective for five years and compared to other medical therapies is much cheaper over 5 years although it becomes expensive if the device is removed before that time limit. Therefore any adverse events are important on two accounts. Firstly, heavy menstrual bleeding is a long term symptom and hence necessitates a long term treatment. Secondly, the adverse side effect may lead to premature removal of the levonorgestrel-releasing intrauterine system hence reducing its cost effectiveness.

The adverse events of interest fall into two categories; those related to an intrauterine device such as pelvic infection, dysmenorrhoea, irregular bleeding, ectopic pregnancy and expulsion of the device and those related to progestogens such as bloating, weight gain and breast tenderness.

The levonorgestrel-releasing intrauterine system releases 20ug per day of levonorgestrel and so drug-related adverse events are assumed to be less frequent than with the oral preparations which result in higher serum concentrations. One trial comparing LNG IUS with NET (Irvine 1998) has found no significant difference in the rate of progestogenic adverse events. However, another trial comparing LNG IUS with TCRE (Crosignani 1997) has reported a higher rate of side effects most of which were progestogenic in the women with the LNG IUS in situ. Three trials have reported expulsion of the device within 12 months of 3.3%, 4.6% and 5.9%. There is no evidence of a greater rate of dysmenorrhoea in women with the LNG IUS but in one trial intermenstrual bleeding and breast tenderness were significantly more likely for the women when compared with those women taking NET for 21 days. The small trials included in this review have not reported on rates of pelvic inflammatory disease or ectopic pregnancies but this information can be found in the contraceptive studies of the LNG IUS.

SATISFACTION/ACCEPTABILITY OF TREATMENT

In one trial where LNG IUS is compared with NET taken over 21 days, the LNG IUS is preferred to the latter therapy. Sixty-four percent of the LNG IUS group liked the treatment "well" or "very well" and 77% elected to continue with the treatment at the end of the study compared with 44% and 22% respectively in the NET group. Similarly, 64.3% of women with an LNG IUS cancelled their planned hysterectomy after 6 months of treatment compared with 14.3% of women continuing with their current medical treatment, although womens' preferences may have been affected by the type of intervention. No group differences in satisfaction, however, were shown where LNG IUS was compared with TCRE.

No study has included mortality or resource cost as outcome measures. However, in New Zealand, Mirena costs approximately $5 per month when used for the full time span of 5 years (NHC NZ 1998). No comparative studies have assessed cost effectiveness with other medical or surgical treatments.

HOW CAN THESE RESULTS ANSWER THE ORIGINAL OBJECTIVES OF THIS REVIEW?

1. Progesterone/progestogen-releasing intrauterine systems, both Mirena and Progestasert, are more effective than no treatment for heavy menstrual bleeding. Although these devices have not been

compared to either placebo or no treatment control groups in randomised controlled trials, there is a 90% reduction from baseline in menstrual blood loss for the participants treated with the levonorgestrel-releasing intrauterine system and a smaller reduction ranging from 18 to 71% for Progestasert.
2. There is no statistical evidence of comparative efficacy with the Progestasert system and other therapy. The levonorgestrel-releasing intrauterine system is more effective than cyclical progestogens but significantly less effective than transcervical resection of the endometrium in reducing heavy menstrual bleeding, as assessed by the semi-quantitative pictorial bleeding assessment chart. However, the levonorgestrel-releasing intrauterine system has not been compared to other commonly used medical therapies such as the combined contraceptive pill, cyclical hormone replacement, NSAIDs and tranexamic acid. Direct comparisons may not have been considered necessary since none of the above mentioned medical therapies are known from objective measurements in RCTs to reduce the MBL by more than 50% compared to the reduction in MBL by the LNG IUS of 90% or greater.
3. Clear evidence is lacking that the LNG IUS is associated with greater improvements in quality of life measures when compared with other therapy.
4. The LNG IUS is associated with a higher rate of intermenstrual bleeding and breast tenderness than oral progestogens given for 21 days and also a higher rate of progestogenic side effects than TCRE.
5. The LNG IUS is more acceptable as a treatment for heavy menstrual bleeding than norethisterone taken for 21 days of the cycle and women are also more satisfied with their treatment but there are no differences in satisfaction rate when it is compared with transcervical resection of the endometrium.
6 The cost effectiveness of progesterone/progestogen-releasing intrauterine systems cannot be commented on within the context of the results available.

AUTHORS' CONCLUSIONS

Implications for practice

The levonorgestrel-releasing intrauterine system results in a significant reduction from baseline in heavy menstrual bleeding (in both RCTs and non-randomised studies). It is more effective than cyclical norethisterone taken for 21 days but not as effective as TCRE. It is uncertain if this objective change in blood loss is reflected in any significant improvement in subjective symptoms of heavy menstrual bleeding but the system is more acceptable to women than oral progestogens taken for 21 days. The levonorgestrel-releasing intrauterine system is associated with a greater rate of progestogenic adverse events and intermenstrual bleeding but rates of dysmenorrhoea do not appear to differ. We cannot comment on the risk of pelvic infection, ectopic pregnancy or cost effectiveness.

Implications for research

The results in this review are based on a very small number of participants. Additional RCTs are needed to test the efficacy of progestogen/progesterone-releasing intrauterine systems compared to other medical therapies for heavy menstrual bleeding. Future trial design needs to plan a longer period of follow-up (ideally, 5 years) to adequately assess effectiveness and adverse events and include outcomes such as cost effectiveness, quality of life and participant satisfaction and acceptability. It would also be useful to assess whether these agents reduce menstrual blood loss in women with self reported heavy menstrual bleeding and not the highly selected population presented here that have clinically defined menorrhagia.

POTENTIAL CONFLICT OF INTEREST

There is no conflict of interest to declare.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Cameron 1987
Methods	Randomisation computer generated and assignment in sealed envelopes. Single centre, parallel group design with no blinding. Number of participants randomised: n=30. No withdrawals/exclusions reported. No power calculation. Intention to treat analysis. Source of funding, Birthright Research Grant, RCOG.
Participants	Women, aged between 29 and 50, recruited from Royal Infirmary, Edinburgh, UK. Inclusion criteria: MBL>50 ml/cycle. No exclusion criteria stated.
Interventions	Rx 1: Norethisterone, 5mg bds, days 15-25 of cycle. Rx 2: Danazol, 200mg, daily.

	Rx 3: Mefenamic acid, 500mg tds, for first 5 days of menstruation. Rx 4: Progesterone releasing IUS, 65ug progesterone daily. Duration: 2 cycles.
Outcomes	Menstrual blood loss (alkaline haematin method). Duration of menstruation (days).
Notes	Groups not comparable at baseline. Baseline MBL in danazol group significantly greater than in mefenamic acid and progesterone IUS groups. Original data not available from principal author; MBL data reported as median and range. Median substituted for mean in meta-analysis and standard deviation estimated from the range.
Allocation concealment	B

Study	**Crosignani 1997**
Methods	Computer generated randomisation with consecutively numbered opaque sealed envelopes. Blinding not discussed for clinician or statistician and not possible for the participant. Exclusions post randomisation: 0. Losses to follow-up: 6 months = 0, 12 months = 1.
Participants	Country: Italy Number of women randomised = 70 Aged 38-53 years, all referred for a hysterectomy because of heavy menstrual bleeding Inclusion criteria: > 80 mls / 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 menstual blood loss, concomitant illness, Hb<10g/dl.
Interventions	Levonorgestrel-releasing (20ug/day) intrauterine contraceptive system inserted within seven days of menstruation versus endometrial resection in the early proliferative phase using a rollerball and a 90 degree loop. All the resections were performed by the same surgeon.
Outcomes	Menstrual blood loss by pictorial charts and history at 6 and 12 months follow-up Hb and serum Fe at 6 and 12 months Participant satisfaction as very satisfied, satisfied, uncertain, dissatisfied 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.
Allocation concealment	A

Study	**Irvine 1998**
Methods	Computer generated randomisation with consecutively numbered opaque sealed envelopes. Blinding not discussed for clinician or statistician and not possible for participant. Exclusions post randomisation: 0. Losses to follow-up: 3 months = 3.
Participants	Country: UK Number of women randomised = 44 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 MBL < 80 mls, 62 declined to do MBL measurements, 4 declined to participate)

	Inclusion criteria: > 80 mls / 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	Levonorgestrel-releasing (20ug/day) intrauterine contraceptive system inserted within seven days of menstruation versus Norethisterone 5 mg three times daily taken on Day 5-26 of the menstrual cycle for three cycles.
Outcomes	Menstrual blood loss by alkaline haematin method for pretreatment, first and third month of use. 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 intention to treat analysis of data.
Allocation concealment	A

Study	**Kittelsen 1998**
Methods	Sealed opaque sequentially numbered identical envelopes for randomisation. Single centre, parallel group design with no blinding. 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) No power analysis for sample size performed and no analysis by intention to treat. Source of funding: Not stated.
Participants	Country: Norway Premenopausal women aged 30 to 49 years with heavy menstrual bleeding recruited from a gynaecology clinic specialising in operative hysteroscopy. Inclusion criteria: premenopausal (FSH>40mIU/mL and 17B oestradiol<0.2nmol/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
Outcomes	PBAC score 12 months after treatment
Notes	Study has been extended to 36 months.
Allocation concealment	A

Study	**Lahteenmaki 1998**
Methods	Randomisation table balanced in blocks of 4 and concealment ensured by sealed envelopes.

	Multicentre (3), parallel group with no blinding (open, phase III). Power calculation performed for sample size but actual numbers of women accrued fell short of the number required for adequate power (power of the study is only 70%). Intention to treat analysis for main outcome only. Number of women randomised = 56 Number of withdrawals = 3 Source of funding: Leiras, Finland.
Participants	Country: Finland Women with spontaneous menstrual cycles and scheduled to undergo hysterectomy for treatment of excessive uterine bleeding with or without dysmenorrhoea and prepared to accept another conservative attempt at treatment. Exclusions: fibroid > 3cm in diameter or > 3 uterine fibroids as assessed by ultrasonography, history or current clinical evidence or suspicion of malignancy or active liver disease, adnexal tumours or cysts, or pelvic inflammatory disease within the previous 12 months.
Interventions	Treatment: LNG IUS (Mirena) inserted after menstruation Control: Continuation with existing medical treatment for heavy menstrual bleeding or dysmenorrhoea or both. Duration: 6 months
Outcomes	Main outcome: willingness to continue the current treatment instead of hysterectomy at 6 months (not considered in this review) Number of days of menstrual bleeding Quality of life measures (VAS scores)
Notes	The study design is likely to have affected womens' attitudes towards continuation of treatment and/or quality of life. One group was randomised to a new treatment, LNG IUS, and the other group to continuation of their existing treatment and there was no blinding. This is likely to have affected qualitative assessments by the women causing a bias in favour of the "new" treatment.
Allocation concealment	A

Characteristics of excluded studies

Study	Reason for exclusion
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 so the study did not fulfill the inclusion criteria.

Characteristics of ongoing studies

Study	Read 1999
Trial name or title	Mirena Study
Participants	Women with menorrhagia
Interventions	Mirena intrauterine system
Outcomes	Patient satisfaction Changes in menstrual cycle
Starting date	01/01/1996
Contact information	Mr Michael Read The Orchard Centre

Characteristics of ongoing studies (*Continued*)

	Gloucestershire Royal NHS Trust Great Western Rd Gloucester GL1 3NN Tel: +44 1452 395 548 Fax: +44 1452 395 556
Notes	Completion date: 01/01/2001 Study located on the National Research Register

Study	**Rogerson 1999**
Trial name or title	Smart Study
Participants	Women with heavy menstrual bleeding
Interventions	(1) Mirena intrauterine system (2) Transcervical resection of the endometrium
Outcomes	Patient satisfaction at 12 months Symptomatic changes Requirement for repeat treatment Health related quality of life Adverse events Cost effectiveness
Starting date	1999
Contact information	L. Rogerson Department of Obstetrics and Gynaecology Gledhow Wing St James University Hospital Leeds LS9 7TF
Notes	Total follow up of 5 years

GRAPHS

Comparison 01. IUS VERSUS PLACEBO OR NO TREATMENT

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mean menstrual blood loss (mls)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
02 Mean reduction in menstrual blood loss (mls)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
03 Amenorrhoea (greater than three months)	0	0	Peto Odds Ratio 95% CI	Not estimable
04 Women's perceived blood loss (better or same/worse)	0	0	Peto Odds Ratio 95% CI	Not estimable
05 Pictorial blood chart score	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
06 Duration of loss (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
07 Number of Sanitary pads/cycle	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
09 Quality of life scores	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
18 Proportion of women with side effects	0	0	Peto Odds Ratio 95% CI	Not estimable

19 Side effects - Pelvic inflammatory events	0	0	Peto Odds Ratio 95% CI	Not estimable
20 Side effects - Pregnancy events	0	0	Peto Odds Ratio 95% CI	Not estimable
21 Side effects - Menstrual pelvic pain	0	0	Peto Odds Ratio 95% CI	Not estimable
22 Side effects - Menstrual irregularity/intermenstrual bleeding	0	0	Peto Odds Ratio 95% CI	Not estimable
23 Side effects - Progestogenic	0	0	Peto Odds Ratio 95% CI	Not estimable
24 Withdrawal from treatment because of adverse events	0	0	Peto Odds Ratio 95% CI	Not estimable
25 Proportion who find the treatment unacceptable	0	0	Peto Odds Ratio 95% CI	Not estimable
26 Mortality	0	0	Peto Odds Ratio 95% CI	Not estimable

Comparison 02. IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mean menstrual blood loss (mls)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
02 Mean reduction in blood loss (mls)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
03 Amenorrhoea (greater than three months)	1	35	Peto Odds Ratio 95% CI	8.67 [1.52, 49.35]
04 Proportion of women satisfied with treatment	1	40	Peto Odds Ratio 95% CI	2.13 [0.62, 7.33]
05 Pictorial blood chart score	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
06 Duration of loss (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
07 Number of sanitary pads/cycle	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
08 Proportion where MBL interfered with quality of life after treatment	1	31	Peto Odds Ratio 95% CI	2.12 [0.42, 10.79]
09 Proportion of women with side effects	0	0	Peto Odds Ratio 95% CI	Not estimable
10 Side effects - Pelvic inflammatory events	0	0	Peto Odds Ratio 95% CI	Not estimable
11 Side effects - Mood swings	1	31	Peto Odds Ratio 95% CI	1.22 [0.28, 5.24]
12 Side effects - Menstrual pelvic pain	0	0	Peto Odds Ratio 95% CI	Not estimable
13 Side effects - Intermenstrual bleeding/menstrual irregularity	1	31	Peto Odds Ratio 95% CI	4.34 [1.01, 18.66]
14 Side effects - Breast tenderness	1	31	Peto Odds Ratio 95% CI	9.11 [2.20, 37.79]
15 Withdrawal from treatment because of adverse events	1	44	Peto Odds Ratio 95% CI	0.37 [0.07, 1.82]
16 Proportion who find the treatment unacceptable	1	40	Peto Odds Ratio 95% CI	0.12 [0.03, 0.40]
17 Proportion of women willing to continue with alternative treatment rather than undergo planned hysterectomy	1	56	Peto Odds Ratio 95% CI	7.84 [2.71, 22.69]
18 Mortality	0	0	Peto Odds Ratio 95% CI	Not estimable

19 Descriptive results where data cannot be pooled		Other data	No numeric data

Comparison 03. IUS VERSUS ANY SURGICAL TREATMENT

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Mean menstrual blood loss (mls)	1	60	Weighted Mean Difference (Fixed) 95% CI	12.24 [-1.86, 26.34]
02 Mean reduction in menstrual blood loss (mls)	1	60	Weighted Mean Difference (Fixed) 95% CI	27.20 [16.83, 37.57]
03 Success of treatment (PBAC score <75)	0	0	Peto Odds Ratio 95% CI	Not estimable
04 Amenorrhoea (greater than three months)	2	129	Peto Odds Ratio 95% CI	0.39 [0.18, 0.83]
05 Proportion of women satisfied with treatment	1	69	Peto Odds Ratio 95% CI	0.38 [0.08, 1.79]
06 Pictorial blood chart score	2	113	Weighted Mean Difference (Fixed) 95% CI	18.55 [2.36, 34.73]
07 Duration of loss (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
08 Number of sanitary pads/cycle	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
09 Proportion of women with side effects	1	69	Peto Odds Ratio 95% CI	3.43 [1.32, 8.91]
10 Side effects - Pelvic inflammatory events	0	0	Peto Odds Ratio 95% CI	Not estimable
11 Side effects - Pregnancy events	0	0	Peto Odds Ratio 95% CI	Not estimable
12 Side effects - Menstrual pelvic pain	1	69	Peto Odds Ratio 95% CI	2.05 [0.21, 20.38]
13 Side effects - Menstrual irregularity/intermenstrual bleeding	1	69	Peto Odds Ratio 95% CI	11.26 [3.27, 38.75]
14 Side effects - Progestogenic	0	0	Peto Odds Ratio 95% CI	Not estimable
16 Mortality	0	0	Peto Odds Ratio 95% CI	Not estimable
17 Quality of life (QOL) scores at 12 mths (SF36) - descriptive results			Other data	No numeric data

INDEX TERMS

Medical Subject Headings (MeSH)

*Intrauterine Devices, Medicated; Levonorgestrel [administration & dosage; *therapeutic use]; Menorrhagia [*drug therapy]; Progesterone [administration & dosage; *therapeutic use]; Progesterone Congeners [administration & dosage; *therapeutic use]

MeSH check words

Female; Humans

COVER SHEET

Title Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Authors Lethaby AE, Cooke I, Rees M

Contribution of author(s)	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. 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. 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.
Issue protocol first published	1996/3
Review first published	2000/2
Date of most recent amendment	15 November 2004
Date of most recent SUBSTANTIVE amendment	25 June 1999
What's New	First published with Anne as the lead reviewer in Issue 2, 2000. The protocol stage had been written by Inez Cooke.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
DOI	10.1002/14651858.CD002126
Cochrane Library number	CD002126
Editorial group	Cochrane Menstrual Disorders and Subfertility Group
Editorial group code	HM-MENSTR

GRAPHS AND OTHER TABLES

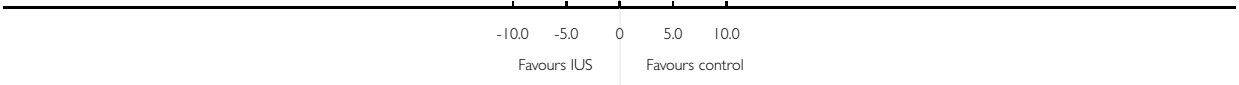
Comparison 03. 01 Mean menstrual blood loss (mls)

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 01 Mean menstrual blood loss (mls)

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Comparison 03. 02 Mean reduction in menstrual blood loss (mls)

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 02 Mean reduction in menstrual blood loss (mls)

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 03 Amenorrhoea (greater than three months)

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 03 Amenorrhoea (greater than three months)

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

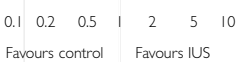
Comparison 03. 04 Women's perceived blood loss (better or same/worse)

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 04 Women's perceived blood loss (better or same/worse)

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Comparison 03. 05 Pictorial blood chart score

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 05 Pictorial blood chart score

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

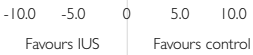
Comparison 03. 06 Duration of loss (days)

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 06 Duration of loss (days)

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Comparison 03. 07 Number of Sanitary pads/cycle

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 07 Number of Sanitary pads/cycle

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 09 Quality of life scores

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 09 Quality of life scores

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 18 Proportion of women with side effects

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 18 Proportion of women with side effects

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 19 Side effects - Pelvic inflammatory events

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 19 Side effects - Pelvic inflammatory events

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 20 Side effects - Pregnancy events

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 20 Side effects - Pregnancy events

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 21 Side effects - Menstrual pelvic pain

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 21 Side effects - Menstrual pelvic pain

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 22 Side effects - Menstrual irregularity/intermenstrual bleeding

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 22 Side effects - Menstrual irregularity/intermenstrual bleeding

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 23 Side effects - Progestogenic

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 23 Side effects - Progestogenic

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 24 Withdrawal from treatment because of adverse events

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 24 Withdrawal from treatment because of adverse events

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 25 Proportion who find the treatment unacceptable

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 25 Proportion who find the treatment unacceptable

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 26 Mortality

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 01 IUS VERSUS PLACEBO OR NO TREATMENT

Outcome: 26 Mortality

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

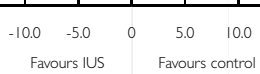
Comparison 03. 01 Mean menstrual blood loss (mls)

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 01 Mean menstrual blood loss (mls)

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



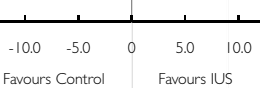
Comparison 03. 02 Mean reduction in blood loss (mls)

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 02 Mean reduction in blood loss (mls)

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Comparison 03. 03 Amenorrhoea (greater than three months)

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 03 Amenorrhoea (greater than three months)

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Irvine 1998	6/19	0/16		100.0	8.67 [1.52, 49.35]
Total (95% CI)	19	16		100.0	8.67 [1.52, 49.35]
Total events: 6 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.43 p=0.01					

Comparison 03. 04 Proportion of women satisfied with treatment

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 04 Proportion of women satisfied with treatment

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Irvine 1998	14/22	8/18		100.0	2.13 [0.62, 7.33]
Total (95% CI)	22	18		100.0	2.13 [0.62, 7.33]
Total events: 14 (Treatment), 8 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.20 p=0.2					

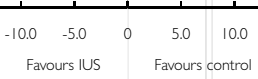
Comparison 03. 05 Pictorial blood chart score

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 05 Pictorial blood chart score

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Comparison 03. 06 Duration of loss (days)

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 06 Duration of loss (days)

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 07 Number of sanitary pads/cycle

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 07 Number of sanitary pads/cycle

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

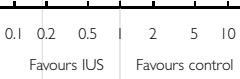
Comparison 03. 08 Proportion where MBL interfered with quality of life after treatment

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 08 Proportion where MBL interfered with quality of life after treatment

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Irvine 1998	6/19	2/12		100.0	2.12 [0.42, 10.79]
Total (95% CI)	19	12		100.0	2.12 [0.42, 10.79]
Total events: 6 (Treatment), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.91 p=0.4					



Comparison 03. 09 Proportion of women with side effects

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 09 Proportion of women with side effects

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 10 Side effects - Pelvic inflammatory events

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 10 Side effects - Pelvic inflammatory events

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

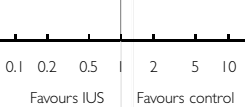
Comparison 03. 11 Side effects - Mood swings

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 11 Side effects - Mood swings

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Irvine 1998	12/19	7/12		100.0	1.22 [0.28, 5.24]
Total (95% CI)	19	12		100.0	1.22 [0.28, 5.24]
Total events: 12 (Treatment), 7 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.26 p=0.8					



Comparison 03. 12 Side effects - Menstrual pelvic pain

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 12 Side effects - Menstrual pelvic pain

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 13 Side effects - Intermenstrual bleeding/menstrual irregularity

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 13 Side effects - Intermenstrual bleeding/menstrual irregularity

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Irvine 1998	10/19	2/12		100.0	4.34 [1.01, 18.66]
Total (95% CI)	19	12		100.0	4.34 [1.01, 18.66]
Total events: 10 (Treatment), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.97 p=0.05					

Comparison 03. 14 Side effects - Breast tenderness

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 14 Side effects - Breast tenderness

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Irvine 1998	14/19	2/12		100.0	9.11 [2.20, 37.79]
Total (95% CI)	19	12		100.0	9.11 [2.20, 37.79]
Total events: 14 (Treatment), 2 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.04 p=0.002					

Comparison 03. 15 Withdrawal from treatment because of adverse events

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 15 Withdrawal from treatment because of adverse events

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Irvine 1998	2/22	5/22		100.0	0.37 [0.07, 1.82]
Total (95% CI)	22	22		100.0	0.37 [0.07, 1.82]
Total events: 2 (Treatment), 5 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.22 p=0.2					

Comparison 03. 16 Proportion who find the treatment unacceptable

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 16 Proportion who find the treatment unacceptable

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Irvine 1998	5/22	14/18		100.0	0.12 [0.03, 0.40]
Total (95% CI)	22	18		100.0	0.12 [0.03, 0.40]
Total events: 5 (Treatment), 14 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.42 p=0.0006					

Comparison 03. 17 Proportion of women willing to continue with alternative treatment rather than undergo planned hysterectomy

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 17 Proportion of women willing to continue with alternative treatment rather than undergo planned hysterectomy

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Lahteenmaki 1998	18/28	4/28		100.0	7.84 [2.71, 22.69]
Total (95% CI)	28	28		100.0	7.84 [2.71, 22.69]
Total events: 18 (Treatment), 4 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.80 p=0.0001					

Comparison 03. 18 Mortality

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 02 IUS VERSUS ANY OTHER MEDICAL TREATMENT

Outcome: 18 Mortality

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 19 Descriptive results where data cannot be pooled

Descriptive results where data cannot be pooled

Study		
Cameron 1987	MENSTRUAL BLOOD LOSS AFTER 2 CYCLES OF TREATMENT: IUS group: median 55mls, range 31-75mls, n=8 Norethisterone group: median 106mls, range 24-216, n=8 Mefenamic acid group: median 51mls, range 45-203mls, n=8 Danazol group: median 54mls, range 30-347mls, n=6 Treatment groups were not comparable at baseline and there were no statistical tests comparing the after	NUMBER OF DAYS OF MENSTRUAL BLEEDING AFTER 2 CYCLES OF TREATMENT: IUS group: median 10 days, range 7-13 days Norethisterone group: median 5 days, range 3-7 days Mefenamic acid group: median 5 days, range 4-7 days Danazol group: median 4 days, range 2-6 days No statistical tests were performed comparing values between groups.

Descriptive results where data cannot be pooled (*Continued*)

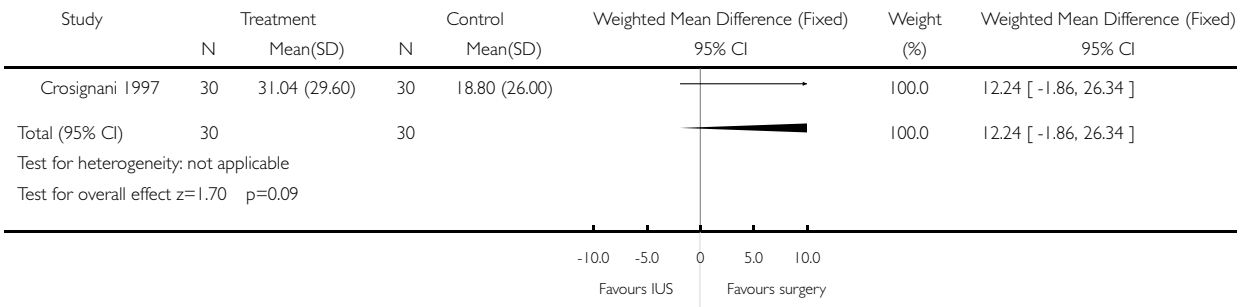
Study		
	treatment values between groups.	
Irvine 1998	MENSTRUAL BLOOD LOSS AFTER 3 CYCLES OF TREATMENT (Intention to treat): LNG IUS group - Median 6mls, range 0-284mls NET group - Median 20mls, range 4-137mls Wilcoxon rank-sum test: t=315.5, p=0.033	MEDIAN REDUCTION IN MENSTRUAL BLOOD LOSS AFTER 3 CYCLES OF TREATMENT: LNG group - Median: 104, range: minus108 - 733 NET group - Median 94, range 56 - 209 Two sample t test: t=0.58, p=0.56
Lahteenmaki 1998	NUMBER OF DAYS OF MENSTRUAL BLEEDING 6 MONTHS AFTER TREATMENT: LNG group: median 2 days, 5th-95th centile 0-13 days Medical treatment group: median 5 days, 5th-95th centile 2-8 days Differences in the number of days of bleeding between groups did not reach statistical significance.	VAS SCORES FOR 5 ITEMS OF QUALITY OF LIFE (AT 6 MONTHS): General well being: LNG Group: median 24, range 14-40 Medical treatment group: median 79, range 64-87 Wilcoxon test: p<0.001 Work performance: LNG group: median 20, range 5-35 Medical treatment group: median 76, range 54-87 Wilcoxon test: p<0.001 Physical activity: LNG group: median 27, range 9-38 Medical treatment group: median 78, range 55-88 Wilcoxon test: p<0.001 Sex life: LNG group: median 36, range 17-49 Medical treatment group: median 66, range 51-85 Wilcoxon test: p=0.002 Leisure time activity: LNG group: median 11, range 5-27 Medical treatment group: median 74, range 54-86 Wilcoxon test: p<0.001

Comparison 03. 01 Mean menstrual blood loss (mls)

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 03 IUS VERSUS ANY SURGICAL TREATMENT

Outcome: 01 Mean menstrual blood loss (mls)



Comparison 03. 02 Mean reduction in menstrual blood loss (mls)

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 03 IUS VERSUS ANY SURGICAL TREATMENT

Outcome: 02 Mean reduction in menstrual blood loss (mls)

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Crosignani 1997	30	-116.80 (18.40)	30	-144.00 (22.40)		100.0	27.20 [16.83, 37.57]
Total (95% CI)	30		30			100.0	27.20 [16.83, 37.57]
Test for heterogeneity: not applicable							
Test for overall effect z=5.14 p<0.00001							

Comparison 03. 03 Success of treatment (PBAC score <75)

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 03 IUS VERSUS ANY SURGICAL TREATMENT

Outcome: 03 Success of treatment (PBAC score <75)

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 04 Amenorrhoea (greater than three months)

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 03 IUS VERSUS ANY SURGICAL TREATMENT

Outcome: 04 Amenorrhoea (greater than three months)

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Crosignani 1997	6/34	9/35		44.0	0.63 [0.20, 1.95]
Kittelsen 1998	11/30	21/30		56.0	0.27 [0.10, 0.73]
Total (95% CI)	64	65		100.0	0.39 [0.18, 0.83]
Total events: 17 (Treatment), 30 (Control)					
Test for heterogeneity chi-square=1.20 df=1 p=0.27 I=17.0%					
Test for overall effect z=2.46 p=0.01					

Comparison 03. 05 Proportion of women satisfied with treatment

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 03 IUS VERSUS ANY SURGICAL TREATMENT

Outcome: 05 Proportion of women satisfied with treatment

Study	IUS n/N	Surgery n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Crosignani 1997	29/34	33/35		100.0	0.38 [0.08, 1.79]
Total (95% CI)	34	35		100.0	0.38 [0.08, 1.79]
Total events: 29 (IUS), 33 (Surgery)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.23 p=0.2					

Comparison 03. 06 Pictorial blood chart score

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 03 IUS VERSUS ANY SURGICAL TREATMENT

Outcome: 06 Pictorial blood chart score

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Crosignani 1997	30	38.80 (37.10)	30	23.50 (32.60)		83.8	15.30 [-2.37, 32.97]
Kittelsen 1998	24	42.00 (99.70)	29	6.60 (15.00)		16.2	35.40 [-4.86, 75.66]
Total (95% CI)	54		59			100.0	18.55 [2.37, 34.73]
Test for heterogeneity chi-square=0.80 df=1 p=0.37 I =0.0%							
Test for overall effect z=2.25 p=0.02							

Comparison 03. 07 Duration of loss (days)

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 03 IUS VERSUS ANY SURGICAL TREATMENT

Outcome: 07 Duration of loss (days)

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 08 Number of sanitary pads/cycle

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 03 IUS VERSUS ANY SURGICAL TREATMENT

Outcome: 08 Number of sanitary pads/cycle

Study	Treatment N Mean(SD)	Control N Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

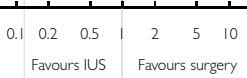
Comparison 03. 09 Proportion of women with side effects

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 03 IUS VERSUS ANY SURGICAL TREATMENT

Outcome: 09 Proportion of women with side effects

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Crosignani 1997	19/34	9/35		100.0	3.43 [1.32, 8.91]
Total (95% CI)	34	35		100.0	3.43 [1.32, 8.91]
Total events: 19 (Treatment), 9 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.53 p=0.01					



Comparison 03. 10 Side effects - Pelvic inflammatory events

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 03 IUS VERSUS ANY SURGICAL TREATMENT

Outcome: 10 Side effects - Pelvic inflammatory events

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 11 Side effects - Pregnancy events

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 03 IUS VERSUS ANY SURGICAL TREATMENT

Outcome: 11 Side effects - Pregnancy events

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Comparison 03. 12 Side effects - Menstrual pelvic pain

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 03 IUS VERSUS ANY SURGICAL TREATMENT

Outcome: 12 Side effects - Menstrual pelvic pain

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Crosignani 1997	2/34	1/35		100.0	2.05 [0.21, 20.38]
Total (95% CI)	34	35		100.0	2.05 [0.21, 20.38]
Total events: 2 (Treatment), 1 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.61 p=0.5					

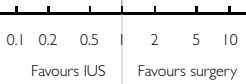
Comparison 03. 13 Side effects - Menstrual irregularity/intermenstrual bleeding

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 03 IUS VERSUS ANY SURGICAL TREATMENT

Outcome: 13 Side effects - Menstrual irregularity/intermenstrual bleeding

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Crosignani 1997	12/34	0/35		100.0	11.26 [3.27, 38.75]
Total (95% CI)	34	35		100.0	11.26 [3.27, 38.75]
Total events: 12 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.84 p=0.0001					



Comparison 03. 14 Side effects - Progestogenic

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 03 IUS VERSUS ANY SURGICAL TREATMENT

Outcome: 14 Side effects - Progestogenic

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

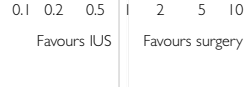
Comparison 03. 16 Mortality

Review: Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding

Comparison: 03 IUS VERSUS ANY SURGICAL TREATMENT

Outcome: 16 Mortality

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
Total (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Comparison 03. 17 Quality of life (QOL) scores at 12 mths (SF36) - descriptive results

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

Study	Quality of Life
Crosignani 1997	SF 36 SCORES ONE YEAR AFTER TREATMENT: Physical functioning: LNG IUS: Median 85.0, (Interquartile range (IQR) 62.8-95.0) TCRE: Median 90.0, (IQR 71.9-94.7) Social functioning: LNG IUS: Median 75.0, (IQR 50.0-87.5) TCRE: Median 75.0, (IQR 56.2-87.5) Role limitation (physical) LNG IUS: Median 100.0, (IQR 50.0-100.0) TCRE: Median 100.0, (IQR 50.0-100.0) Role limitation (emotional): LNG IUS: Median 66.7, (IQR 33.3-100.0) TCRE: Median 100.0, (IQR 66.7-100.0) Bodily pain: LNG IUS: Median 41.0. (IQR 41.0-84.0) TCRE: Median 72.0, (IQR 55.0-92.0) General health perception: LNG IUS: Median 65.0, (IQR 51.0-79.5) TCRE: Median (IQR) 72.5 (64.5-77.0) Vitality: LNG IUS: Median 55.0, (IQR 47.5-65.0) TCRE: Median 55.0, (IQR 40.0-70.0) Mental health: LNG IUS: Median 60.0, (IQR 46.0-68.0) TCRE: Median 64.0, (IQR 46.7-68.0)