Effectiveness Bulletin

Managing menorrhagia

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Menorrhagia – excessive regular menstrual blood loss – is one of the most common reasons for gynaecological referral¹ and is the main presenting problem in at least half of all women having hysterectomies.² Referral and treatment rates vary widely, nationally and internationally,^{3,4} reflecting uncertainty about the most appropriate management.

Two population studies showed that average blood loss is between 30 and 40 ml; in 90% of the population the loss is less than 80 ml,^{5,6} leading to the widely accepted clinical definition of menorrhagia as blood loss of 80 ml or more per menstrual period. Although objective measurement of blood loss is possible,⁷ it is confined to research uses and is not currently considered to be routinely feasible in clinical practice.

In a national survey 31% of the women described their blood loss as heavy.⁸ However, many women who seek treatment for heavy bleeding in reality do not have higher than average menstrual blood loss.^{5,9,10,11} In one population study 26% of women with blood loss well within the normal range (< 60 ml) considered their loss heavy and 40% of those with objectively heavy losses (> 80 ml) considered their loss as moderate or light.⁵ In one study in Scotland over half the women referred for endometrial ablation for dysfunctional uterine bleeding had menstrual blood loss less than 80 ml.¹²

This paper reviews the evidence of the effectiveness of management options for menorrhagia. Searches were undertaken on Medline, Embase, and several other databases, including that of the Research Council for Complementary Medicine, to identify the relevant research reports and were supplemented by consultation with experts and manual cross checking of reference lists. Drug trials without objective measures of menstrual blood loss were excluded. The searches identified 31 randomised controlled trials of drug treatments which included objective measurement of menstrual blood loss and three randomised controlled trials of surgical interventions, comparing abdominal hysterectomy with hysteroscopic surgical procedures. A discussion of the quality of studies appears in *Effective Health Care* Bulletin No 9.

Effectiveness of management options

REASSURANCE

It is difficult for women to judge how their experience of menstrual blood loss compares

with that of others. Although a woman's perception of the heaviness of loss and its effect on her quality of life are the major reasons for seeking medical help, she might benefit from being reassured that her experience is not abnormal or from being offered counselling.¹³ The effectiveness of giving reassurance and counselling is not known but is currently being studied within a randomised controlled trial in Oxford.

DIAGNOSIS

Dilatation and curettage is often carried out on women with menorrhagia for diagnostic purposes, primarily to exclude the rare but important possibility of an endometrial malignancy.^{4,14} The operation commonly entails general anaesthesia and a two day hospital stay, although the Audit Commission has estimated that up to 86% of these procedures could be performed as day cases.¹⁵

Management options for menorrhagia

- Reassurance
- Diagnosis
- Drug treatments
- Surgical treatments

The use of dilatation and curettage for diagnosing endometrial malignancy is not cost effective in women aged under 40 years because serious disease and the prevalence of endometrial cancer are so uncommon in these women.¹⁶⁻²² Based on estimates of endometrial cancer incidence of 0.66 per 100 000 women aged 30-34, Vessey *et al* calculated that between 3000 and 4000 of these procedures would have to be performed to detect one case of endometrial cancer in women aged under 35.¹⁷ This minimal potential benefit needs to be considered in the context of the risks associated with dilatation and curettage, such as those associated with general anaesthesia and uterine perforation and laceration of the cervix.^{16,18,23} In addition, several studies indicated that an appreciable proportion of endometrial lesions are not detected by dilatation and curettage.^{16,17,24,25}

Other methods of investigating the lining of the uterus – endometrial sampling – have become available, such as the use of narrow curettes, vacuum curettes, catheters or cannulas, endometrial washing, and endometrial scraping or aspiration. Hysteroscopy – that is, the insertion of a small magnifying

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instrument through the vagina and cervix to allow viewing of the inside of the uterus – can be used on its own or with one of the sampling techniques to achieve a more accurate diagnosis.^{26–28} These newer methods of endometrial sampling are commonly performed in outpatient clinics or general practice surgeries. They seem to have high levels of patient acceptability, lower complication rates, and do not require inpatient admission and general anaesthesia.^{24 28–57} However, no randomised controlled trial has been carried out to compare outpatient endometrial sampling and dilatation and curettage.

In the only economic assessment of the diagnostic technologies that has been performed – namely, a cost analysis of hysteroscopy versus dilatation and curettage in the Australian health service – it emerged that if outpatient hysteroscopy were to replace dilatation and curettage performed either as a day case or inpatient procedure an appreciable cost saving to the health service would result.⁵⁸ However, these savings are unlikely to be realised if the possible increase in the rate of investigation is not controlled.

DRUG TREATMENTS

Menorrhagia can be treated by drugs in primary care. A wide variety of drugs are used, ranging from non-steroidal anti-inflammatory drugs, antifibrinolytics, hormones, and intra-uterine devices. Each year around £7m is spent in the United Kingdom on primary care prescribing to treat menorrhagia.⁵⁹ However, the effectiveness of many of the drug treatments is uncertain.^{60 61}

A summary of the features of the drug trials performed for menorrhagia can be found at the end of the article (table 1), with the reduction in loss of menstrual blood reported for each arm of the trials (figure). Since these results are derived from different trials, comparison across the trials, while suggestive, is not a reliable indicator of relative effectiveness since the participating patients are not always comparable. These comparisons indicate that the levonorgestrel releasing intrauterine device,^{62–66} danazol,^{65–69} tranexamic acid, (J Bonnar, paper presented at the Royal Society of Medicine, London, 1994)^{70–74} mefenamic acid (J Bonnar, paper presented at the Royal Society of Medicine, London, 1994),^{65 66 69 75 76} and naproxen^{76–79} may be the most efficacious in reducing menstrual blood loss. Norethisterone, particularly at low doses and used for short duration,^{65 66 80 81} seems to be the least efficacious and may be ineffective for reducing blood loss. Of the more efficacious drugs, the hormone releasing coil is not yet registered for use in the United Kingdom as a treatment for menorrhagia. The serious side effects of danazol and its high cost make it unacceptable for long term use. Early reports of an increase in risk of thromboembolic clots after use of tranexamic acid, which led to restrictions of its use in the United Kingdom, have now been discounted.⁸² Mefenamic acid has fewer side effects and the advantage of alleviating menstrual pain.

This evidence is only suggestive, as insufficient randomised controlled trials have been performed which directly compare the top ranking drugs. However, in one randomised controlled trial tranexamic acid showed a 58% reduction in loss of menstrual blood compared with 28% for mefenamic acid (J Bonnar, paper presented to Royal Society of Medicine, London, 1994). In another, tranexamic acid showed a 45% reduction compared with a 20% increase with low doses of norethisterone.⁸¹

These results are in stark contrast to the current patterns of prescribing. Based on a national sample of 518 general practitioners who treated 4603 patients complaining of menorrhagia, norethisterone (apparently one of the least effective drugs) was the most commonly used drug, prescribed to 38% of the patients, followed by mefenamic acid (27%), combined oral contraceptives (11%), combined hormone replacement therapy (8%), dydrogesterone (6%), danazol (6%), ethamsylate (6%) and tranexamic acid (5%).⁵⁹

SURGICAL TREATMENTS

Three main types of surgical procedures are used to treat menorrhagia: dilatation and curettage, removal of the uterus and cervix (hysterectomy), and removal of the lining of the womb (endometrial ablation).

Dilatation and curettage has been widely used as a possible treatment option for menorrhagia but has never been shown to be effective.^{22 24} No published reports exist of randomised controlled trials of this procedure against a placebo treatment. Reports from uncontrolled case studies claiming a beneficial effect lack objective measurement of blood loss. The only study to measure blood loss before and after dilatation and curettage found that blood loss returned to its previous level or higher by the second subsequent menstrual period.⁹

Hysterectomy is the most commonly used surgical treatment for menorrhagia, which can be performed through the abdomen or through the vagina and, more recently, laparoscopically. The new procedures of endometrial ablation or resection with laser surgery or diathermy are designed to remove as much of the uterine lining as possible. Rates of endometrial ablation and resection are increasing. Figures from an audit undertaken by the Royal College of Obstetrics and Gynaecology of endometrial resection or ablation in the United Kingdom (in the National Health Service (NHS) or private sector) indicate that from 1 April 1993 to 31 October 1994 about 10 200 procedures were undertaken, 82% of which used diathermy (transcervical resection of the endometrium or rollerball or a combination of both), 16% used laser surgery alone, and 2% radiofrequency or cryoablation.⁸³

Hysterectomy is one of the most commonly performed surgical operations: in England in 1993–4, 73 517 women had this operation in NHS hospitals.⁸⁴ Since many hysterectomies are performed in private hospitals this figure underestimates the total number of women

undergoing the procedure. Large socioeconomic variations exist for the likelihood of women having a hysterectomy for menstrual reasons.⁸⁵⁻⁸⁶ There are three randomised controlled trials which compared abdominal hysterectomy with newer, less invasive surgical interventions for menorrhagia (table 2) (M J Sculpher *et al*, personal communication, 1995).⁸⁷⁻⁹⁰

Hysterectomy requires longer time in theatre and results in a longer length of stay than the less invasive approaches. Abdominal hysterectomy has a high complication rate of around 45%, including pain, haemorrhage, wound infection, urinary retention, urinary tract infection, and vaginal discharge (M J Sculpher *et al*, personal communication, 1995).⁸⁷⁻⁹⁰ This compares with a rates of 0–15% for resection or ablation, with reported complications of uterine perforation, fluid overload, haemorrhage, and urinary tract infection. Lower complication rates have been reported for vaginal hysterectomy in uncontrolled studies.⁹¹⁻⁹³ To reduce the rate of serious postoperative infections preoperative antibiotics should be used routinely. A meta-analysis of 25 trials of antibiotic prophylaxis during abdominal hysterectomy suggests a possible reduction in postoperative infections from 21% to 9%.⁹⁴

As the uterus is removed in a hysterectomy the ending of menstrual periods is guaranteed. Endometrial resection or ablation, on the other hand, is not always successful in reducing menstrual blood loss, and blood loss and pain may increase with time after endometrial ablation.⁹⁵ Relatively high rates of reoperation after the initial treatment with endometrial resection or ablation have been reported, ranging from 6–23%, with the higher rates being reported in studies with longer follow up.^{87-90 96-102} These studies include repeat resection or ablation or hysterectomy, or both. Another cohort study estimates the cumulative probability of requiring a hysterectomy four years after endometrial resection as 12% after total resection and 40% after repeat total resection.¹⁰³

High levels of satisfaction have been reported for both types of surgical procedures but seem higher after hysterectomy than resection or ablation. In terms of health related quality of life as measured by the rating scale of the EuroQol[®] instrument, the initial advantage at one month after the operation of transcervical resection of the endometrium is offset by four months after the operation,⁸⁹ the difference being non-significant.

As endometrial resection uses less operating theatre time and requires a shorter length of hospital stay its health service costs are less than those for abdominal hysterectomy.⁸⁹ However, this initial cost advantage may diminish over time because a substantial proportion of women receiving resection subsequently have a repeat resection or a hysterectomy, or both.

Oophorectomy is often performed at the same time as abdominal hysterectomy to eliminate the risk of ovarian cancer. Whether or not this practice is justified depends on the balance of risks and benefits in terms of years

of life gained and quality of life. If the ovaries are removed a premenopausal women will have undergone a "surgical menopause," with a consequent increased risk of osteoporosis and cardiovascular disease. However, removal of the ovaries also seems to reduce the risk of breast cancer.¹⁰⁴ Overall, oophorectomy reduces average life expectancy in younger women by at least five years if they did not take hormone replacement therapy.¹⁰⁵ Since many women do not comply with long term hormone replacement therapy the routine removal of healthy ovaries in women who are not at high risk of ovarian cancer is hard to justify.¹⁰⁶

Conclusions

As many women complaining of heavy periods may not in fact have excessive menstrual blood loss every attempt should be made to ascertain whether blood loss is indeed high. However, this is difficult without a routinely available method of objective measurement. It is also important to determine what particular problems heavy periods cause the women. Reassurance may help improve subjective assessments of blood loss and discomfort and reduce the need for treatment.

All the treatment options should be discussed with the woman, giving her sufficient information about the risks and benefits of drug and surgical interventions for her to make an informed choice about management options.

Dilatation and curettage for diagnosis should generally not be offered to women under 40 years. Endometrial sampling, with or without hysteroscopic examination, is probably more cost effective for diagnosing uterine abnormalities in older women and can be carried out as an outpatient procedure.

General practitioners should consider offering a course of effective drug treatment such as tranexamic acid and mefenamic acid to women as a first line treatment. Drug use should be monitored to identify prescribing of apparently ineffective drugs such as norethisterone.

There is no obvious best surgical treatment for all women. The advantage of conservative surgery over abdominal hysterectomy in the short term seems not to be sustained in the longer term. Dilatation and curettage should not be used as a treatment for menorrhagia. If newer, less invasive surgical techniques are used, it is important to ensure that the surgeons have the necessary training and skills. Purchasers should monitor indications for treatment among their provider units, the use of dilatation and curettage in diagnosis, and prescribing patterns.

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Table 1 Randomised controlled trials of drug treatment of menorrhagia*

Trial	Selection criteria	Intervention	Outcome measures	Duration	Results (change in menstrual blood loss; side effects)
Fraser <i>et al</i> 1981 ⁷⁵	Women with convincing history of menorrhagia, enrolled through radio/television discussion. Subjective. No pretreatment control cycles Trial: crossover, double blind Size: A = 30, B = 39, C = 14	Mefenamic acid (500 mg three times daily) during period and placebo Group A: > 80 ml Group B: < 80 ml Group C: < 35 ml	Menstrual blood loss, menstrual symptoms, pain, pad and tampon usage, side effects	4 Months (2 months each) 19% Dropout	Mefenamic acid 28% reduction for all women, 30% for > 80 ml, 19% for < 80 ml Side effects: no significant differences between mefenamic acid and placebo
Van Eijkeren <i>et al</i> 1992 ¹⁰⁷	Women under 45 years scheduled for hysterectomy, menstrual blood loss > 80 ml. One pretreatment control cycle Trial: double blind Size: A = 6, B = 5	Group A: mefenamic acid (500 mg three times daily from 5 days before period until bleeding ceases) Group B: placebo Hysterectomy during second menstruation	Menstrual blood loss	2 Months 42% Dropout	Mefenamic acid 40% reduction v 25% increase for placebo group Side effects: mefenamic acid: stomach pains 1, itching 2, placebo: headache 1, itching 1
Muggeridge and Elder 1983 ¹⁰⁸	Menstrual blood loss > 75 ml Trial: crossover, double blind Size: N = 15	Mefenamic acid (500 mg three times daily started at onset of period) and placebo	Menstrual blood loss, dysmenorrhoea	4 Months (2 months each) 25% Dropout	Mefenamic acid 30% reduction, placebo 12% reduction Side effects: incidence low, no difference between groups

Table 1 continued

Trial	Selection criteria	Intervention	Outcome measures	Duration	Results (change in menstrual blood loss; side effects)
Guillebaud <i>et al</i> 1978 ¹⁰⁹	Healthy, parous women using IUDs. Menstrual blood loss measured before entry Trial: crossover, single blind Size: A = 15, B = 10	Mefenamic acid (500 mg twice daily from onset till bleeding ceased) and placebo Group A: > 80 ml Group B: < 80 ml	Menstrual blood loss, duration of menses, side effects	4 Months 34% Dropout	Group A: mefenamic acid 34% reduction; group B: mefenamic acid 23% reduction Side effects: indigestion 1, headaches and dizziness 1 (both withdrew)
Bonnar (paper presented at Royal Society of Medicine meeting, London, 1994)	Menstrual blood loss > 80 ml Trial: double blind Size: A = 27, B = 25, C = 29	Treatment for 5 days during cycle Group A: tranexamic acid (1 g four times daily) Group B: mefenamic acid (500 mg three times daily) Group C: ethamsylate (500 mg four times daily)	Menstrual blood loss, side effects	3 Months 27% Dropout	Group A: 58% reduction; group B: 25% reduction; group C: 0% reduction Side effects: A = 4, B = 5, C = 13
Fraser and McCarron 1991 ¹¹⁰	Convincing clinical history of menorrhagia Trial: crossover (2 drugs each), not blinded Size: A = 15, B = 15, C = 15	Group A: mefenamic acid and naproxen (500 mg, 250 mg for 5 days) Group B: mefenamic acid and oral contraception (low dose once daily 21 days) Group C: mefenamic acid and danazol (200 mg once daily from day 5 of cycle) All groups: mefenamic acid 500 mg three times daily or four times daily on days 1 to maximum of 5	Menstrual blood loss	6 Months 16% Dropout	Mefenamic acid 31% reduction, naproxen 12% reduction, oral contraceptives 43% reduction and danazol; 50% reduction Side effects: not reported
Cameron <i>et al</i> 1990 ⁸⁰	Menstrual blood loss > 80 ml Trial: random allocation to either treatment Size: A = 17, B = 15	Group A: mefenamic acid (500 mg three times daily on days 1–5 of period) Group B: norethisterone (5 mg twice daily on days 19–26 of cycle)	Menstrual blood loss, duration, side effects	2 Months 0% Dropout	Mefenamic acid 24% reduction, norethisterone 20% reduction Side effects: mefenamic acid 10, norethisterone 11, including headache, abdominal pain, and nausea
Hall <i>et al</i> 1987 ⁷⁶	Dysfunctional uterine bleeding. Menstrual blood loss measured before entry Trial: crossover, double dummy Size: A = 18, B = 18	Group A: naproxen sodium (550 mg initially then 275 mg four times daily for 5 days) then mefenamic acid (500 mg three times daily) Group B: mefenamic acid then naproxen sodium	Menstrual blood loss, patient and doctor preferences, side effects	4 Months 15% Dropout	Mefenamic acid 46% reduction, naproxen sodium 47% reduction Side effects: gastrointestinal (nausea, diarrhoea, abdominal discomfort, and anorexia): naproxen sodium 13, mefenamic acid 6; central nervous system (light headedness, dizziness, tiredness, and headache): mefenamic acid 6, naproxen sodium 5
Dockeraey <i>et al</i> 1989 ⁹⁹	Menstrual blood loss > 80 ml Trial: not clear if blinded Size: A = 19, B = 20	Group A: mefenamic acid (500 mg three times daily for 3–5 days beginning of period) Group B: danazol (100 mg twice daily for 60 days beginning last day of period)	Menstrual blood loss, dysmenorrhoea, side effects, patient acceptability	2 Months 3% Dropout	Mefenamic acid 22% reduction, danazol 56% reduction Side effects: mefenamic acid 11 events, danazol 51 events
Cameron <i>et al</i> 1987, ⁶⁵ Cameron 1989 ⁶⁶	Menstrual blood loss > 50 ml Trial: random allocation Size: A = 6, B = 8, C = 8, D = 8	Group A: danazol (200 mg once daily) Group B: mefenamic acid (500 mg three times daily for days 1–5 of period) Group C: norethisterone (5 mg twice daily from day 15–25 of cycle) Group D: progestasert coil (releasing 65 µg progesterone daily)	Menstrual blood loss, prostaglandin measurement	2 Months 0% Dropout	Danazol 71% reduction, mefenamic acid 25% reduction, norethisterone increase 12%, progestasert coil 23% reduction Side effects: not reported
Chamberlain <i>et al</i> 1991 ¹¹¹	Women aged 18–55, with regular cycles and menstrual blood loss > 80 ml Trial: double dummy, double blind, allocation by minimisation Size: A = 16, B = 18	Group A: ethamsylate (500 mg four times daily during period) Group B: mefenamic acid (500 mg three times daily during period)	Menstrual blood loss, side effects	4 Months 23% Dropout	Ethamsylate 20% reduction, mefenamic acid 24% reduction Side effects: ethamsylate 5, mefenamic acid 10 (abdominal discomfort, headache most common)
Callender <i>et al</i> 1970 ⁷⁰	Women and anaemia, complaining of menorrhagia with no abnormality Trial: crossover, double blind Size: n = 16	Tranexamic acid (500 mg four times daily for first 4 days of period) Placebo	Menstrual blood loss (Oxford total body counter), duration, number of pads, side effects	6 Months 20% Dropout	Tranexamic acid 36%, placebo 6% reduction Side effects: tranexamic acid 2, placebo 2
Vermeylen <i>et al</i> 1968 ⁷¹	History of menorrhagia. Subjective Trial: crossover, double blind Size: n = 16	Tranexamic acid (500 mg 4 hourly from day 1 till bleeding stops) Placebo	Mean haemoglobin loss, pads used, side effects	6 Months 36% Dropout	Tranexamic acid 35% reduction. No blood loss reported, just percentage Side effects: no difference between groups
Nilsson and Rybo 1967 ⁷²	Women aged 15–49 with suspected menorrhagia. Subjective Trial: crossover, double blind Size: n = 36	Low dose tranexamic acid (250 mg 4 hourly) High dose tranexamic acid (500 mg 4 hourly) Placebo	Menstrual blood loss, side effects	3 Months 0% Dropout	Low dose tranexamic acid 38% reduction, high dose 51% reduction, placebo 8% reduction Side effects: Low dose 7, high dose 13, placebo 8 (mainly diarrhoea and abdominal pain)

Table 1 continued

Trial	Selection criteria	Intervention	Outcome measures	Duration	Results (change in menstrual blood loss; side effects)
Ylikorkala and Viinikka 1983 ⁷³	Women with intrauterine devices and menstrual blood loss > 70 ml <i>Trial:</i> crossover, double blind <i>Size:</i> n = 19	Tranexamic acid (1.5 g three times daily for 5 days) Diclofenac sodium (50 mg three times daily day 1 and 25 mg three times daily for 4 days)	Menstrual blood loss, duration, intermenstrual bleeding, side effects, restricted activity, pelvic pain, subjective assessment	5 Months 10% Dropout	Tranexamic acid 56% reduction, diclofenac sodium 24% reduction <i>Side effects:</i> tranexamic acid 12, diclofenac sodium 5
Andersch <i>et al</i> 1988 ⁷⁴	Women aged 34–49 with menstrual blood loss > 80 ml <i>Trial:</i> crossover, open <i>Size:</i> n = 15	Tranexamic acid (1.5 g three times daily for 3 days, 1 g twice daily during days 4 and 5) Flurbiprofen (100 mg twice daily for 5 days)	Menstrual blood loss, duration, side effects	4 Months 0% Dropout	Tranexamic acid 53% reduction, flurbiprofen 24% reduction <i>Side effects:</i> tranexamic acid 7, flurbiprofen 4
Milsom <i>et al</i> 1991 ⁶⁴	Menstrual blood loss > 80 ml and no pelvic pathology <i>Trial:</i> first 20 women given IUD, next 15 randomised to crossover design <i>Size:</i> IUD = 16, drugs 15	IUD group: levonorgestrel IUD (release rate of 20 µg/day) Drugs group: Flurbiprofen (100 mg twice daily for 5 days) crossover with: tranexamic acid (1.5 g three times daily for days 1–3, then 1 g twice daily for days 4 and 5)	Menstrual blood loss, side effects	4 Months 11% Dropout	IUD: 82% reduction at 3 months, 88% reduction at 6 months, 96% reduction at 12 months Drugs: flurbiprofen 21% reduction and tranexamic acid 44% reduction <i>Side effects:</i> tranexamic acid 7, flurbiprofen 4
Chimbira <i>et al</i> 1980 ⁶⁷	Women referred to gynaecology outpatient clinics with menstrual blood loss > 60 ml <i>Trial:</i> single blind <i>Size:</i> A = 8, B = 16, C = 16	Group A: placebo Group B: danazol (200 mg once daily for 12 weeks) Group C: danazol (100 mg once daily for 12 weeks)	Menstrual blood loss, duration, side effects	5 Months 0% Dropout	Danazol (200 mg) 86% reduction, danazol 100 mg 75% reduction, placebo no change <i>Side effects:</i> tiredness 5, musculoskeletal pain 4, skin rashes 3, headaches 6, irritability 3, vaginitis 3, average weight gain 2.3 kg
Makarainen and Ylikorkala 1986 ¹¹²	Women complaining of excessive menstrual bleeding and primary menorrhagia > 70 ml menstrual blood loss. No pretreatment control cycle <i>Trial:</i> double blind, crossover <i>Size:</i> n = 13	High dose: Ibuprofen (400 mg three times daily) Low dose: Ibuprofen (200 mg three times daily) Placebo	Menstrual blood loss, duration, pain, side effects	3 and 6 Months 23% Dropout	High dose ibuprofen 25% reduction, low dose 16% reduction <i>Side effects:</i> high dose 5 (including headache, dizziness, nausea, diarrhoea, and dyspepsia), low dose 6
Roy and Shaw 1981 ¹¹³	Healthy volunteers who had used IUD for at least 5 months with no side effects. Subjective. One pretreatment control cycle <i>Trial:</i> double blind, cross over <i>Size:</i> n = 20	Ibuprofen (400 mg four times daily) Placebo	Menstrual blood loss	2 Months 0% Dropout	Ibuprofen, overall 32% reduction, placebo 6% increase. Mean values not given <i>Side effects:</i> ibuprofen 2 (swelling around eyes and mouth, mild stomach cramps), placebo 2 (mild stomach cramps and nausea, headaches, and dizziness)
Kasonde and Bonnar 1975 ¹¹⁴	Women complaining of excessive menstrual bleeding while using intrauterine devices <i>Trial:</i> open <i>Size:</i> A = 11, B = 12	Group A: ethamsylate (500 mg four times daily during period) Group B: EACA (3 g four times daily during period)	Menstrual blood loss	4 Months 8% Dropout	Ethamsylate 7% reduction, EACA 50% reduction <i>Side effects:</i> not reported
Harrison and Campbell 1976 ¹¹⁵	Women with primary menorrhagia. IUD users also recruited. One pretreatment control cycle. <i>Trial:</i> double blind, crossover <i>Size:</i> A = 9, B = 13	Ethamsylate (500 mg four times daily five days before onset and for 10 days) Placebo Group A: primary menorrhagia Group B: IUD users	Menstrual blood loss, side effects	4 Months 29% Dropout	Ethamsylate 50% reduction in primary menorrhagia group, 19% reduction IUD group, no change for placebo group <i>Side effects:</i> reported in 18/53 ethamsylate cycles and 17/50 placebo cycles but reportedly not serious
Rybo <i>et al</i> 1981 ⁷⁷	Women with primary menorrhagia. Women without primary menorrhagia were fitted with IUD <i>Trial:</i> double blind, cross over <i>Size:</i> A = 4, B = 5, C = 5	Naproxen (500 mg in morning, then 250 mg in afternoon for 2 days, then 250 mg twice daily for up to 7 days) Placebo Group A: primary menorrhagia Group B: IUD and menstrual blood loss > 80 ml Group C: IUD and menstrual blood loss < 80 ml	Menstrual blood loss	4 Months 0% Dropout	Group A: naproxen 24% reduction Group B: 38% reduction Group C: 9% reduction Placebo: 2–4% reduction <i>Side effects:</i> not reported
Davies <i>et al</i> 1981 ⁷⁸	Women using IUDs and menstrual blood loss > 80 ml <i>Trial:</i> double blind, crossover <i>Size:</i> n = 34	High dose: naproxen (500 mg twice daily, plus 250 mg once daily for 5 days) Low dose: naproxen (500 mg loading dose then 250 mg three times daily for 5 days)	Menstrual blood loss, pads and tampons used, intensity of bleeding, assessment of drug effect, side effects	4 Months 29% Dropout	High dose 32% reduction, low dose 22% reduction <i>Side effects:</i> no adverse reactions to naproxen, 1 patient with nausea/vomiting
Ylikorkala and Pekonen 1986 ⁷⁹	Menstrual blood loss > 80 ml <i>Trial:</i> double blind, crossover <i>Size:</i> n = 14	Naproxen (250 mg four times daily for days 1–5 of cycle) Placebo	Menstrual blood loss, duration, side effects	4 Months 0% Dropout	Naproxen 36% reduction, placebo 11% increase <i>Side effects:</i> mild side effects with placebo 1, none with naproxen
Gallegos <i>et al</i> 1978 ⁸³	Women volunteers selected from those requesting an IUD. Menstrual blood loss measured but all < 80 ml. One or two pretreatment control cycles <i>Trial:</i> IUDs randomly allocated <i>Size:</i> A = 7, B = 10, C = 10, D = 7	Group A: UPS-40 (releases 40 µg/day progesterone) Group B: UPS-65 (releases 65 µg/day progesterone) Group C: Norethisterone IUD (releases 10 µg/day progesterone) Group D: Levonorgestrel IUD (releases 2 µg/day of progesterone)	Menstrual blood loss	6 Months 0% Dropout	UPS-40 34% increase (not significant), UPS-65 40% reduction, norethisterone releasing IUD 33% reduction, and levonorgestrel releasing IUD 47% reduction <i>Side effects:</i> not given

Table 1 continued

Trial	Selection criteria	Intervention	Outcome measures	Duration	Results (change in menstrual blood loss; side effects)
Nilsson 1977 ⁶²	Women volunteers from hospital staff, not menorrhagic Trial: random allocation to IUD Size: A = 10, B = 9	Group A: d-norgestrel-releasing IUD (releases 25 µg daily) Group B: copper IUD	Menstrual blood loss	3 Months 0% Dropout	d-norgestrel-releasing IUD 60% reduction Side effects: none given
Vargyas <i>et al</i> 1987 ¹¹⁶	Women aged 16–42 with menstrual blood loss > 60 ml Trial: double blind, crossover Size: n = 29	Meclofenamate sodium (100 mg three times daily for 6 days or until bleeding ceased) Placebo	Menstrual blood loss, duration, dysmenorrhoea, side effects, pads and tampons used	4 Months 9% Dropout	Meclofenamate sodium 49% reduction, placebo 4% reduction Side effects: dysmenorrhoea, backache, headache less severe on active drug, nausea and vomiting; no difference between groups
Higham and Shaw 1993 ⁶⁸	Women aged 20–50 with proved menorrhagia Trial: single blind Size: A = 17, B = 19, C = 18	Group A: danazol (dose reduced each cycle: 200 mg, 100 mg, 50 mg once daily) Group B: danazol (200 mg once daily) Group C: Norethindrone (5 mg three times daily days 19–26)	Menstrual blood loss, duration, interval between cycles, dysmenorrhoea, subjective assessment, side effects	3 Months (4 months after treatment) 24% Dropout	Danazol reducing dose 28% reduction, 200 mg dose 40% reduction Side effects: reducing dose 15 women, 200 mg dose 17, placebo 11
Ingemanson <i>et al</i> 1991 ¹¹⁷	Women using IUDs and menstrual blood loss > 80 ml Trial: double blind, crossover Size: n = 9	Diclofenac (50 mg three times daily for 5 days of period) Placebo	Menstrual blood loss, duration, subjective assessment, side effects	4 Months 0% Dropout	Diclofenac 29% reduction, placebo 4% reduction Side effects: None attributed to diclofenac
Preston <i>et al</i> 1995 ⁸¹	Women complaining of menorrhagia, actual menstrual blood loss > 80 ml Trial: double blind Size: A = 25, B = 21	Group A: tranexamic acid (1 g four times daily, days 1–4) Group B: norethisterone (5 mg twice daily on days 19–26)	Menstrual blood loss, subjective assessment, side effects	2 Months 9% Dropout	Tranexamic acid 45% reduction, norethisterone 20% increase Side effects: tranexamic acid 8 headaches and 3 gastric, norethisterone 10 headache and 7 gastric

*All trials included at least 2 pretreatment control cycles except if otherwise indicated.
EACA = *e*-amino caproic acid.
IUD = intrauterine device.

Table 2 Randomised controlled trials of surgical treatment of menorrhagia

Trial	Selection criteria	Outcome measures	Follow up	Results
Dwyer <i>et al</i> 1993 ⁸⁸ Sculpher <i>et al</i> 1993 ⁸⁹ Sculpher <i>et al</i> , personal communication 1995	Women aged < 52 (mean 40) years complaining of menorrhagia which could not be controlled by conservative means and who were candidates for hysterectomy, attending the gynaecological department of Bristol's teaching hospital Exclusions: women with uterine size > 12 weeks, additional symptoms or other disease made hysterectomy the preferred treatment. Histological assessment of the endometrium was undertaken if hyperplasia due to anovulatory menstruation was suspected 196 of 216 women found suitable and agreeing to participate randomly allocated 2 groups A: abdominal hysterectomy (97) B: endometrial resection (99) Note: 43(44%) in group A <i>v</i> 34(34%) in group B had preintervention GHQ scores of ≥ 12	Requirement for analgesia; complications; postoperative recovery time; menstrual status; sexual activity; psychiatric morbidity using the 60 item general health questionnaire Self recording of degree of pain each day for a week; booklet recording postoperative problems, amount and duration of vaginal bleeding, date of return to work and normal daily activities Failure rate of endometrial resection, as assessed by the number of women not satisfied or who had severe synechiae Degree of satisfaction with operation 4 months after operation Restricted version of EuroQol [®] health questionnaire, completed a minimum of 4 months after the operation, asking the women to value their health on average, 1 month before and 2 weeks after the operation, and at the time of completing the questionnaire SF 36 questionnaire completed as part of longer term follow-up together with the EuroQol [®] questionnaire	4 Months, with a 2% dropout rate 69% completed the EuroQol [®] health questionnaire sent at 4 months after the operation At an average of 2.2 years, loss to follow up: Group A: 25% Group B: 17%	Postoperative morbidity, length of stay and time taken to return to work, normal daily activities, and sexual intercourse were significantly lower in the endometrial group. Premenstrual symptoms, symptoms of dysmenorrhoea, bloating and breast tenderness were less frequent after hysterectomy. After endometrial resection, 13 women were amenorrhoeic while 76 had hypomenorrhoea 46(47%) of the women having a hysterectomy had complications compared to 4(4%) of those having an endometrial resection. Only one woman having a hysterectomy did not require analgesia for postoperative pain compared with 39 of the endometrial resection group After 4 months there was a significant difference in satisfaction in favour of hysterectomy (94% <i>v</i> 85 being very satisfied or satisfied with the results of their treatment) and no significant difference in EuroQol [®] scores At 4 months there was failure rate of at least 10–15% in those in whom endometrial resection appeared complete. At 2.8 years the cumulative probability of a repeat resection was 12% and of a hysterectomy 16%, an overall 23%
Gannon <i>et al</i> 1991 ⁸⁷	Women aged 29–51 (median 40) years awaiting abdominal hysterectomy for menorrhagia at Royal Berkshire Hospital Reading, found suitable after history, physical examination, and pelvic ultrasonography with a vaginal probe Exclusions: women known to have leiomyomata, endometrial or cervical neoplasia, concomitant ovarian disease, pelvic inflammatory disease, or endometriosis 51 of 78 women without pelvic pathology on the waiting list and consenting to participate, allocated randomly to 2 groups: A: abdominal hysterectomy (26) B: endometrial resection (25)	Requirement for analgesia; complications; postoperative recovery time; menstrual status Diary record of symptoms after discharge from hospital, noting first day without analgesic drugs, date felt fit to return to work Women requiring hysterectomy or a repeat hysteroscopic procedure	9–16 Months (mean 12 months) Loss to follow up: not reported	Recovery after endometrial resection was substantially shorter (median 16 days) than for hysterectomy (median 58 days). Twelve (46%) women in the hysterectomy group had complications, and none of the women who had endometrial resection. Four (16%) women who had endometrial resection required any postoperative analgesia Four (16%) women had repeat resections; none required a hysterectomy within the mean follow up of one year Mean theatre and ward costs for endometrial resection were £407 and for hysterectomy £1270 Authors point to the need for larger numbers and longer follow up to estimate complications and long term efficacy of endometrial resection

Table 2 continued

Trial	Selection criteria	Outcome measures	Follow up	Results
Pinion <i>et al</i> 1994 ⁽⁹⁾	<p>Women attending general gynaecological clinics at Aberdeen's teaching hospital, aged under 50, weighing under 100 kg, with a clinical diagnosis of dysfunctional uterine bleeding (uterus less than size of a pregnancy of 10 weeks, and normal endometrial history), and who would otherwise have undergone a hysterectomy</p> <p>204 women allocated at random to 3 groups:</p> <p>A: hysterectomy (99)</p> <p>B: endometrial laser ablation (53)</p> <p>C: transcervical resection of endometrium (52)</p> <p>Note: study focuses on a comparison between hysterectomy and hysteroscopic surgery as insufficient power to explore for differences between laser ablation and endometrial resection</p>	<p>Requirements for analgesia; complications; postoperative recovery time; menstrual status; urinary, incontinence, premenstrual and menopausal symptoms and dyspareunia</p> <p>Woman's grading of heaviness and pain for each day of the period</p> <p>Patient satisfaction: "How does your health compare with that a year ago? What effect has the operation had on symptoms? How satisfied are you with the effect of treatment"</p> <p>Women requiring hysterectomy or a repeat hysteroscopic procedure</p> <p>Data collected before randomisation, and at 1, 6, and 12 months after treatment</p>	<p>12 Months</p> <p>Non-attenders for follow up:</p> <p>at 1 month: 5%</p> <p>at 6 months: 12%</p> <p>at 12 months: 9%</p>	<p>Women treated by hysteroscopic surgery had less morbidity and a significantly shorter recovery period than those treated by hysterectomy. Five women in the hysterectomy group had major complications, two from anaesthesia, one from intra-abdominal bleeding, and two had pelvic abscesses. One woman given laser ablation had a small bowel obstruction</p> <p>16% of the women in the hysteroscopic group had a hysterectomy 12 months subsequently; 10% a repeat hysteroscopic procedure; 43% were amenorrhoeic or had only a brown discharge and 33% had light periods</p> <p>After 12 months 89% of the hysterectomy group (78% of the hysteroscopic group) were very satisfied with the effect of surgery; 95%(90%) thought there had been an acceptable improvement in symptoms; 73%(48%) indicated that their health was much better than a year previously</p>

	% Menstrual blood increase											No of patients
	20	10	0	10	20	30	40	50	60	70	80	
Hormone releasing coil					*	*	*	*	*		*	93
Danazol						*	*	**	**	*		109
Tranexamic acid							*	*	*	*	*	172
Mefenamic acid					***	*	*	*	*			282
Naproxen				**	*	*	*	*				133
Ibuprofen		*			*	*	*					76
Ethamsylate			*	*	*	*		*				78
Diclofenac					*							19
Norethisterone	*	*			*							44
Placebo	*	*	*	*	*	*	*	*	*	*	*	188

Estimated change in menstrual blood loss in each arm of different drug trials