

THE EFFECTIVENESS OF THE MIRENA COIL (LEVONORGESTREL-RELEASING INTRAUTERINE SYSTEM) IN MENORRHAGIA

A West Midlands Development and Evaluation Service Report

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About West Midlands Development and Evaluation Service

The West Midlands Development and Evaluation Service (DES) produces rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

About InterTASC

West Midlands DES is a member of InterTASC which is a national collaboration with three other units who do rapid reviews: the Trent Working Group on Acute Purchasing; the Wessex Institute for Health Research and Development; York Centre for Reviews and Dissemination. The aim of InterTASC is to share the work on reviewing the effectiveness and cost-effectiveness of health care interventions in order to avoid unnecessary duplication and improve the peer reviewing and quality control of reports.

Contribution of Authors

Antony Stewart wrote the main report, liaising with researchers and experts to identify unpublished data and obtain views on both the protocol and final report; reviewed the effectiveness data, independently assessing its quality and extracted the data; undertook the economic analysis and the review of the epidemiology and alternative treatments.

This report was completed as part of a systematic review course, run by the Department of Public Health and Epidemiology at the University of Birmingham. Carole Cummins and Rachel Jordan were course tutors and acted as main editors to the report. Wendy Phillips independently assessed the quality of studies and extracted data. Lisa Gold provided advice and assistance on the economic analysis, and read and commented on the full report.

Conflicts of Interest

This work has been undertaken by people funded by the NHS. The authors have received no funding from any sponsor in this work.

**West Midlands Development and Evaluation Committee
Recommendation:**

The recommendation for the effectiveness of the mirena coil (levonorgestrel-releasing intrauterine system) in menorrhagia was:

Limited Support

(The Committee would have “supported” this intervention based on the analysis of cost-effectiveness alone, however, it was decided to reduce this to “limited support” because the Mirena Coil is not licensed for this use and the responsibility must lie with the individual clinician)

Anticipated expiry date: 2002

- This report was completed in December 1999
- The searches were completed in March 1999
- There are ongoing trials in progress assessing the effectiveness and cost-effectiveness of LNG-IUS. At least two of these trials are comparing LNG-IUS with endometrial resection. The results of these should provide the basis for a more precise and reliable estimate of the level of benefits associated with LNG-IUS.

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Summary

- Menorrhagia (heavy blood loss during menstruation) constitutes a considerable problem for many women, resulting in much discomfort, anxiety and disruption in the lives of sufferers. The number and cost of consultations and treatments produce a substantial burden to the NHS.
- Surgical procedures such as hysterectomy and endometrial resection are often used to treat menorrhagia, but these can be costly and traumatic. Menorrhagia can also be treated with drugs, but the effectiveness of many drug therapies is uncertain. The levonorgestrel-releasing intrauterine system (LNG-IUS, trade name MIRENA) was developed primarily as a contraceptive device. Its use has been associated with a reduction in menstrual blood loss which might eventually exceed 90% and has comparatively few side-effects.
- Menorrhagia may be experienced by up to 30% of women of reproductive age and accounts for 60% of consultations for menstrual disorders in general practice. Five percent of women aged 30-49 with heavy menstrual bleeding consult their GP each year, and this condition accounts for around 12% of all gynaecology referrals.
- In 1993, 822,000 prescriptions were written for menorrhagia in England and Wales, costing over £7 million. Two-thirds of hysterectomies and endometrial ablation procedures are carried out in order to treat menorrhagia. According to the manufacturers, a total of 65,000 LNG-IUSs were sold during 1997. It is not currently known how many of these were fitted to treat menorrhagia.
- Studies were included if the population was women with heavy menstrual blood loss (≥ 80 ml per cycle). Ten studies were included, 24 were not as they did not evaluate women with confirmed menorrhagia. Five were controlled trials and five were case series.
- Nine of the ten studies measured menstrual blood loss (MBL), and all showed statistically significant average MBL reductions, ranging from 74% to 97% overall. In the four controlled trials reporting MBL reduction, the range was 79% to 96%.
- The LNG-IUS was more effective at reducing MBL when compared with tranexamic acid (an effective drug). The LNG-IUS performed slightly less well than endometrial resection in two studies, though producing MBL reductions of 79% and 90% respectively, compared to baseline. In one study, 82% of women who used the LNG-IUS were taken off the waiting list for surgery. In another, 64% of women cancelled surgery at 6 months, compared with 14% of control group women.
- The cost of the LNG-IUS is around £99, equating to just under £20 per year with a duration of use of five years. When insertion and annual follow-up costs are taken into account, the LNG-IUS costs £219 in primary care, and £384 in secondary care.
- The LNG-IUS provided in primary care proved cheaper than tranexamic acid or norethisterone at the higher dose. When provided in secondary care, it is more expensive than high dose norethisterone but still cheaper than tranexamic acid.
- Full assessment of the cost-effectiveness of surgery compared with the LNG-IUS would require complex models. The available evidence suggests that the use of the LNG-IUS is likely to reduce waiting lists for surgery.
- The LNG-IUS provides an efficacious, satisfactory and cost-effective choice in the treatment of menorrhagia compared to drug therapies, and may reduce demand for surgical treatment. Precise effectiveness relative to other treatments can only be established in larger, more powerful RCTs.

1 Aims of Review and Question to be Addressed

Menorrhagia (heavy blood loss during menstruation) constitutes a considerable problem for many women, resulting in much discomfort, anxiety and disruption in the lives of sufferers. Where no organic pathology is present, the term dysfunctional uterine bleeding is used.¹ The number and cost of consultations and treatments produce a substantial burden to the NHS.²

Surgical procedures such as hysterectomy and endometrial resection are often used to treat menorrhagia, but these can be costly, traumatic, risky²⁻⁵ and sometimes unnecessary.² Menorrhagia can also be treated with drugs, although the effectiveness of some drug therapies is uncertain.² The drugs used have a range of undesirable side effects,⁶ and may need to be used for long periods.^{1 7 8} Norethisterone, a drug commonly used to treat menorrhagia, has been shown to be ineffective for treating this condition.^{1 2 9-11}

The levonorgestrel-releasing intrauterine system (LNG-IUS, trade name MIRENA) was developed primarily as a contraceptive device, and is licensed only for this purpose at present.¹²

Its use has been associated with a reduction in menstrual blood loss^{2 3 6 13-17} which might eventually exceed 90%,¹⁸⁻²⁰ as well as having other benefits and comparatively few side-effects.¹² The device is licensed for five years effective contraceptive use in the UK.²¹

This review assesses the effectiveness of the LNG-IUS for menorrhagia, by evaluating studies where subjects have confirmed menorrhagia.^{5 18-20 22 24-26 51}

Statement of question:

Does the use of LNG-IUS for menorrhagia result in better outcomes than other treatments for menorrhagia, in terms of reducing menstrual blood loss, patient satisfaction, quality of life and cost-effectiveness?

2 Description of Underlying Health Problem

2.1 Nature of Menorrhagia

Menorrhagia is usually defined as menstrual blood loss (MBL) of 80ml or more, per cycle.²⁷ Actual blood loss reported by women presenting is often less than 80ml,^{10 27 28} making patient distress an important consideration in managing menorrhagia. Factors such as parity and high birthweight of previous children appear to be associated with high MBL.²⁹ A simple measure of MBL exists,³⁰ involving the patient's visual categorisation of their daily MBL as heavy, medium or low, on a pictorial chart. A score is calculated from this, which allows an accurate estimate of actual MBL. This is, however, considered difficult to undertake in normal clinical practice.^{31 32} It is also possible that the MBL of women whose loss is extremely high at presentation may reduce by the time they receive treatment. Most women with menorrhagia have no pelvic or organic pathology (such as carcinoma or pelvic infection),^{2 33} and are therefore diagnosed as having dysfunctional uterine bleeding.

2.2 Epidemiology

Menorrhagia may be experienced by up to 30% of women of reproductive age,³⁴ and accounts for 60% of consultations for menstrual disorders in general practice.³⁵ Five percent of women aged 30-49 consult their GP each year with heavy menstrual bleeding,³⁶ and this condition accounts for around 12% of all gynaecology referrals.³⁷ It is the most common cause of iron deficiency in healthy fertile women.^{18 38}

2.3 Treatment Options

Various methods exist for treating menorrhagia:

2.3.1 Hysterectomy

Hysterectomy is carried out on 60% of women referred to secondary care with menorrhagia.⁴⁰ This operation involves removing the entire uterus, thus producing permanent menstrual cessation. The risk of developing uterine cancer in the future is therefore also eliminated.⁴¹ Hysterectomy is, however, associated with a high level of post-operative complications,³² occasional mortality and is believed to increase the risk of developing other diseases, including urinary incontinence.² Women undergoing this procedure require a period of convalescence before resuming normal activities.² Although hysterectomy is associated with a high level of patient satisfaction and mental well being afterwards,^{2 42-45} it nevertheless carries a risk of morbidity and mortality.^{2 3 5} Evidence showing satisfaction and well being may relate to the absence of heavy periods, rather than the operation itself.

Hysterectomy rates tend to increase with lower social class (for menstrual problems) and also with age.⁴⁶ The cost of hysterectomy is high, averaging £1,060 per operation (range £827-£2,278) in 1993,⁴⁷ with average costs for 1997/98 rising to £1,702.⁴⁸

2.3.2 Endometrial resection

Endometrial resection and laser ablation are also performed for menorrhagia. This procedure uses a variety of techniques including diathermy and laser therapies³² to remove most of the lining of the uterus. It has a lower complication rate than hysterectomy and very little mortality.^{2 49} Despite good levels of patient satisfaction and beneficial effects on mental well being,^{2 23 44 49 50} the operation is not always successful in reducing menstrual bleeding.^{2 44 47 49} Re-operations are relatively common with rates ranging from 11-40%,⁸ and it is estimated that around 30% of women undergoing endometrial resection or ablation will eventually have a hysterectomy.⁵² The cost of the procedure is around half that of hysterectomy, averaging £560 in 1993 (range £421-£1691)⁴⁷ and £547 for 1997/8⁴⁸ (this does not take account of recurrent surgery).

2.3.3 Dilatation & Curettage

Another surgical procedure, Dilatation & Curettage (D&C), has often been used. D&C is often regarded as a diagnostic rather than a therapeutic procedure,^{53 54} and is considered ineffective for the treatment of menorrhagia.^{2 53 54 55} One study reported a reduction in menstrual blood loss in most patients immediately after D&C, but losses generally returned to previous levels or higher by the second cycle.⁵⁵

2.3.4 Drug treatments

It is recommended that GPs should offer women with menorrhagia at least one course of drug therapy, before referral for surgery.^{2 56 61} The use of non-hormonal drugs before referral can result in fewer referrals and surgical procedures.⁶² A number of drugs are used in the treatment of menorrhagia, including non-steroidal anti-inflammatory drugs (NSAIDs), anti-fibrinolytics and hormones. Combinations of oestrogen and progestogen can be useful in the treatment of menorrhagia,^{1 2 56} and are considered particularly suitable for nulliparous women, for whom IUD use is associated with an increased risk of pelvic inflammatory disease and infertility.^{6 34 57} Other treatments such as gamolenic acid, anti-heparin agents and flurbiprofen (a prostaglandin synthetase inhibitor) are also used. Tranexamic acid (an anti-fibrinolytic) is considered the most effective and acceptable drug treatment.^{2 11 58 59} The most often prescribed drug, norethisterone (a progestogen hormone) appears to be ineffective,^{1 2 9-11 56 58} although a recent study has shown it to be more effective at increased dose and duration.²⁰ Costs of these drugs vary,^{2 6 60} some have unpleasant side effects^{1 2 6 60} and may require long-term use.^{1 7 8} The annual cost of the progestogen-only pill is £8-12, with the combined pill at £5-39.⁶³ Costs of drug treatments vary between primary and secondary care, as hospitals often secure bulk discounts.

3 Description of New Intervention

3.1 The LNG-IUS

Recently, a device known as the LNG-IUS (a levonorgestrel releasing IUD) has shown promise in the treatment of menorrhagia. The current version of the LNG-IUS works by delivering 20µg levonorgestrel per day to the inner wall of the uterus,^{16 66-68} continually for at least seven years.^{3 69 70-72} It was originally developed as a contraceptive, and licensed in the UK in 1995.⁷³ Although only licensed for contraception at present,¹² it may be used on a 'named patient' basis for the treatment of menorrhagia.⁷⁴ Its use has been associated with a reduction in menstrual blood loss,^{2 3 6 13-16 56 69} which can eventually exceed 90%.¹⁸⁻²⁰ It may offer an attractive alternative to hysterectomy in women considering surgery for menorrhagia.^{26 75} Earlier versions of the progesterone IUD (the Progestasert) produced reductions in menstrual blood loss^{9 10 76 77} or decreasing lengths of bleeding time,⁷⁸ but used higher dosages of the drug, and were associated with higher rates of ectopic pregnancy.^{3 16 79-82} Previous versions of the LNG-IUS using lower doses of levonorgestrel also reported lower menstrual blood loss.⁸³⁻⁸⁶

3.2 Contraceptive Effectiveness

The device is an effective contraceptive,^{16 71 87-94} the effect of which is reversible.^{3 88-90 92 95 96} Ovulation is not suppressed.^{14 97-99} Contraceptive effectiveness in practice is not related to the age of the user.¹ Expulsion rates are similar to other IUDs,^{3 70} and while ectopic pregnancies do occur,^{100 101} rates are lower than with other IUDs.^{14 81 93 102} Use of the device does not suppress ovulation,^{14 97-99} but reduces endometrial thickness,^{103 104}, causing cervical mucus to become scantier and thicker^{3 12 68} and inhibiting penetration by sperm.^{12 105}

3.3 Other Effects

The LNG-IUS may also protect against pelvic infection,^{3 15 81 82 91 93} and sexually transmitted diseases.^{15 17} Furthermore, it may be effective in the treatment and long term prevention of fibroids,^{15 72} conservation of iron,^{3 15 18 106} as well as the prevention and regression of some types and grades of endometrial hyperplasia.^{15 107 108} There appears to be no effect on blood pressure, carbohydrate metabolism, serum lipids, liver function or coagulation.¹⁴ No differences in cervical cytology have been observed between users of the LNG-IUS and copper IUDs.³ The device may also be useful in the treatment of abnormal bleeding in women receiving hormone replacement therapy.¹⁰⁹⁻¹¹¹

3.4 Side Effects

Apart from changes in menstrual bleeding patterns which are especially prevalent in the early post-insertion months,^{72 82 102 112} reported side-effects include headache and nausea (which normally resolve quickly),^{12 14 113} irregular bleeding,^{12 14 15 102} mastalgia and acne^{14 102} (which normally resolve after a few months),¹² functional ovarian cysts^{12 15 72 82 114} (which are normally asymptomatic and resolve within a few weeks),¹⁵ depression,^{14 102} weight gain^{3 14} and lower abdominal pain.¹² No significant drug interactions have been reported.¹² Unlike patients who receive surgery, women using the LNG-IUS remain active throughout treatment, and do not normally lose time from work, apart from the insertion consultation. The device is contra-indicated for women with suspected pregnancy, unexplained uterine bleeding, current genital infection, severely distorted uterine cavities, current liver disease or serious arterial disease.^{6 12}

It is worth noting that amenorrhoea and altered bleeding patterns may be undesirable or even unacceptable to some women, on cultural or other grounds. Patients using the LNG-IUS may therefore request its removal for these reasons⁹³ and counselling may be appropriate to maximise acceptability and continuation of its use,^{14 68 71 106} particularly prior to insertion. Clinicians need adequate training on insertion techniques to ensure successful performance of the device.¹¹⁵

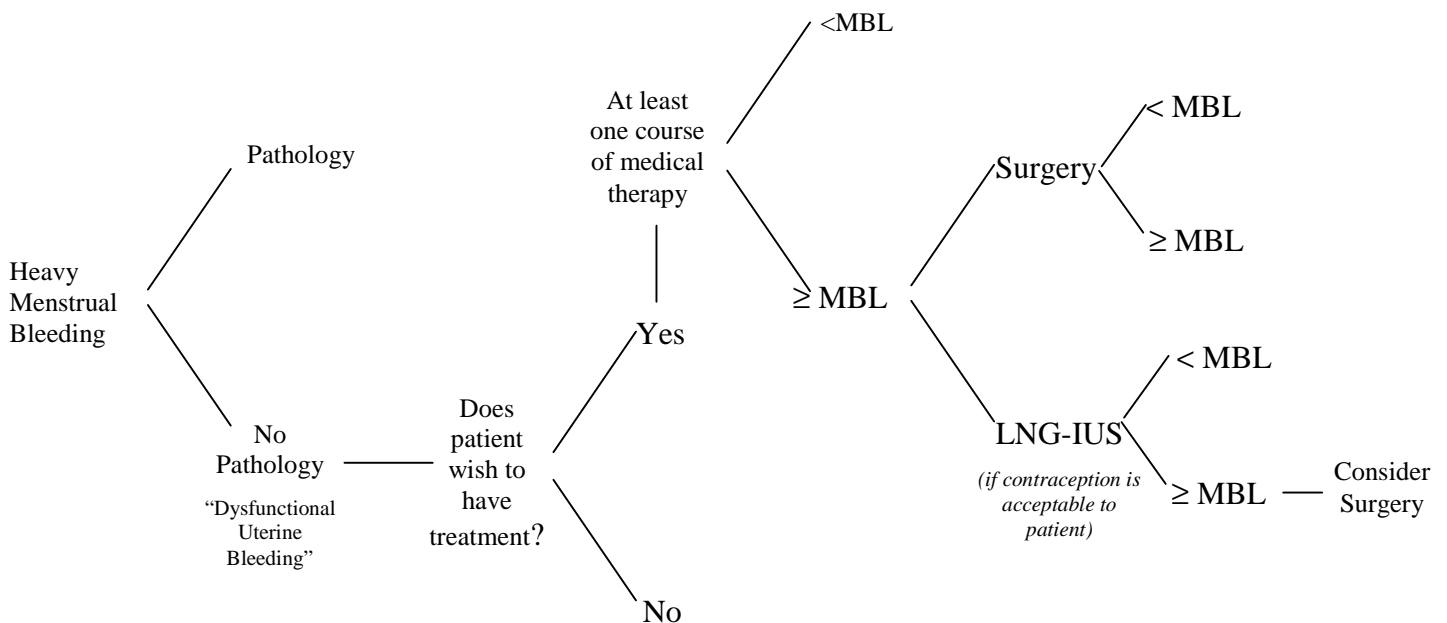
3.5 Licensing

The manufacturers, Schering Health Care, intend to apply to license the use of the LNG-IUS in the UK, both for the treatment of menorrhagia and for hormone replacement therapy. This is, however, unlikely to happen in the short term.

3.6 Treatment Decisions

To aid the assessment of the effectiveness and cost effectiveness of the use of the LNG-IUS for menorrhagia, an explicit statement of events and outcomes was made using the framework of a decision analytic model. The decisions involved in the treatment of women with menorrhagia are illustrated in Figure 1, which aims to be a simple representation of strategies rather than a comprehensive description. Pathology must firstly be excluded, and if dysfunctional uterine bleeding is confirmed, treatment can be commenced, if the patient desires it. It is recommended that at least one course of medical therapy should be tried before considering surgery.² If this is not successful, surgery or the LNG-IUS may be considered. As previously stated, although hysterectomy will produce complete cessation of MBL, endometrial resection may have to be repeated,⁸ and patients may eventually receive hysterectomy.⁵² If LNG-IUS is chosen, contraception must be acceptable to the patient, and surgery may be indicated if MBL is not reduced to levels acceptable to the patient.

Figure 1 - Decision model in the treatment of menorrhagia.



4 Current Service Provision

In 1993, 822,000 prescriptions were written for menorrhagia in England and Wales,³⁹ costing over £7 million.²

During 1992/3, over 73,000 hysterectomies were performed in England,⁶⁴ together with 10,000 endometrial ablations.⁶⁵ During 1997/8, the number of hysterectomies had decreased to 63,345, while endometrial ablations had risen to 36,440.⁴⁸ Two-thirds of these procedures were carried out to treat menorrhagia.² It is estimated that nearly 20% of women will undergo a hysterectomy by the age of 55.⁴⁶

According to the manufacturers, a total of 65,000 LNG-IUSs were sold during 1997. Due to the short time that this intervention has been available, there are no data on its effectiveness in practice. It is not currently known how many of these were fitted to treat menorrhagia, and no data on the proportions used within primary and secondary care are available. There is possibly a wide variation between districts in the numbers of LNG-IUSs fitted.

5 Question of the Review

Does the use of LNG-IUS for menorrhagia result in better outcomes than other treatments for menorrhagia, in terms of reducing menstrual blood loss, patient satisfaction, quality of life and cost-effectiveness?

There is a Cochrane protocol registered by Cooke and Rees, entitled “Progesterone/progestagen releasing IUCDs vs. either placebo or any other medication for heavy menstrual bleeding”.¹¹⁶ The most recent substantive amendment took place in August 1996. Hirsch (1993)¹¹⁷ produced a review entitled “Levonorgestrel IUD for menorrhagia”, concluding that the device was investigational and needed further evaluation. A review of the non-contraceptive use of the LNG-IUS has been published by van den Hurk & O’Brien (1999),¹³¹ but only includes 4 of the 10 studies on women with confirmed menorrhagia evaluated here.

6 Methods of Review

6.1 Search Strategy

The following sources were searched during October and November 1998, followed by a further search in March 1999 to check for more recent papers:

- Medline (via. Pubmed and Ovid)
- Cinahl
- Embase
- Grateful Med
- BMJ Website Archiving Facility
- Cochrane Library
- Best Evidence
- Internet search engines (e.g. Alta Vista, Hot Bot, etc.)
- Reference lists in review articles
- NHS Centre for Reviews and Dissemination (DARE, NEED, HTA)

The following MESH headings and textwords were used:

Menorrhagia, IUD, Hysterectomy, Levonorgestrel, Progestin, Mirena

Appropriate references were also obtained from the following sources:

- Schering Health Care Ltd (manufacturers of the LNG-IUS)
- Royal College of Obstetricians and Gynaecologists Audit Unit
- Hand searching literature available locally (Journal of Family Planning, Diplomat)
- Colleagues, for other published and unpublished data
- Subject Experts

6.2 Inclusion and Exclusion Criteria

No language restrictions were applied. Studies were accepted if they reached the following criteria:

6.2.1 Study Design

All study designs were accepted, but most emphasis was given to controlled clinical trials.

6.2.2 Population

Studies were included if the population was women with heavy menstrual blood loss (≥ 80 ml per cycle). It was important to differentiate between studies evaluating contraceptive efficacy and those carried out expressly to assess the treatment of menorrhagia in women with a confirmed diagnosis. While many of the former report MBL reduction, they were not carried out on women who had menorrhagia. To include them in a review which explicitly focuses on the use of the LNG-IUS in the treatment of menorrhagia would therefore introduce

considerable bias. Studies were excluded if they were not carried out on women with confirmed menorrhagia, or included women with post-menopausal bleeding more than one year from last period, women with contra-indications to LNG-IUS, or LNG-IUS devices releasing doses other than 20µg/day. Study populations included women with confirmed menorrhagia (dysfunctional uterine bleeding), in primary care, secondary care or family planning settings.

6.2.3 Intervention

Studies were included if the interventions were LNG-IUS (20µg/day) alone, or versus placebo or any medical or surgical therapy, or no treatment. As previous versions of the hormonal IUD (which are no longer available in the UK) using different doses of levonorgestrel produced different results, only studies using the current version were included.

6.2.4 Outcomes

Studies were included only if they had outcome information on menstrual blood loss. Ideally, there would also be information on patient satisfaction and acceptability, quality of life and cost effectiveness.

6.3 Data Extraction Strategy

A checklist was used to collect data on each included study, covering the following:

- Study design
- Setting
- Intervention
- Whether menorrhagia was confirmed in subjects
- Outcome measure reported

Two independent reviewers (AS and WP) carried out data extraction, and differences were resolved by discussion.

6.4 Quality Assessment Strategy

Information relating to the quality of included studies was collected, including whether:

- Subjects were randomised to treatment groups
- The randomisation method was specified
 - Inclusion criteria were specified
 - There was clear definition of patient groups
 - Intention to treat analysis was used
 - Loss to follow-up was reported

Two independent reviewers (AS and WP) assessed the quality of studies, and differences were resolved by discussion.

6.5 Data Synthesis

As described in Section 8, it was not possible to combine the data, but the results for each included study were presented.

6.6 Economic Analysis

An economic analysis appears in Section 8.3. This compares the evidence on effectiveness to monthly costs of drug treatments, although comparisons with surgery were not possible. Furthermore, insufficient data on quality of life made it impossible to carry out a cost utility analysis.

7 Results

7.1 Quality and Quantity of Research Available

A total of 34 studies were identified which used the current version of the LNG-IUS and reported menstrual blood loss.^{5 17-20 22 24-26 51 69-72 87 89-91 96 102 104 106 112 118-127 132}

Nine studies were included because they fulfilled all of the inclusion criteria, explicitly evaluating women with confirmed menorrhagia.^{5 18-20 22 24-26 51} Twenty-four studies were not included because although they reported menstrual blood loss reductions in women using the current version of the LNG-IUS, they did not evaluate women with confirmed menorrhagia.^{17 69-72 87 89-91 96 102 104 106 112 118-127} One further study evaluating women with confirmed menorrhagia was identified by a subsequent search.¹³²

The quality characteristics of the ten included studies are summarised in Table 1. Five studies were RCTs and five were case series. Only one was a multicentre study.²⁶ In all of these studies, all subjects had confirmed menorrhagia. Each of the studies clearly defined their patient groups, specified inclusion criteria and reported loss to follow-up and side effects. While the number of side effects was reported, it was not always clear how many women overall had experienced them, as some reported more than one side effect. Amenorrhoea may be perceived as a side effect, depending on the patient's point of view. Outcomes were clearly defined, and baseline MBL was measured prior to the commencement of treatment. The dose of levonorgestrel was stated in all but one of the studies.¹⁹ No subjects were post-menopausal. Each study excluded patients with contraindications to the LNG-IUS.

Of the five controlled trials,^{20 22 26 51 132} four randomised subjects to their treatment groups, and one (Milsom 1991),²² allocated the first 20 consecutive women to the device, and the remaining 15 randomly to drug treatments. Randomisation methods were specified in all trials. Two trials (Milsom 1991, Kittelsen 1998)^{22 132} did not analyse on an intention to treat basis, while another (Crosignani 1997)⁵¹ excluded one LNG-IUS patient from analysis after loss to follow-up at 6 months.

Four of the ten trials reported whole or partial drug company sponsorship.^{19 25 26 51}

Table 1 - Quality assessment

Study	Subjects randomised to treatment groups	Randomisation method specified	Inclusion criteria specified	Clear definition of patient groups	Blinding	Intention to treat	Loss to follow-up reported	Side effects recorded	Outcomes clearly defined	Explicit LNG dose	Confirmed menorrhagia	Baseline MBL measured	Subjects premenopausal	Contra-indications to LNG-IUS observed
Andersson & Rybo (1990) ¹⁸	N/A	N/A	Y	Y	N/A	N/A	Y	Y	Y	Y	Y	Y	Y	Y
Barrington & Bowen-Simpkins (1997) ⁵	N/A	N/A	Y	Y	N/A	N/A	Y	Y	Y	Y	Y	Y	Y	Y
Croignani <i>et al</i> (1997) ⁵¹	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y
Fedele <i>et al</i> (1997) ²⁴	N/A	N/A	Y	Y	N/A	N/A	Y	Y	Y	Y	Y	Y	Y	Y
Irvine <i>et al</i> (1998) ²⁰	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Kittelsen & Istre (1998) ¹³²	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y
Lähteenmäki <i>et al</i> (1998) ²⁶	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Milsom <i>et al</i> (1991) ²²	Y *	Y *	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y
Scholten <i>et al</i> (1989) ²⁵	N/A	N/A	Y	Y	N/A	N/A	Y	Y	Y	Y	Y	Y	Y	Y
Tang & Lo (1995) ¹⁹	N/A	N/A	Y	Y	N/A	N/A	Y	Y	Y	N	Y	Y	Y	Y

* Only subjects in the cross-over arm of the study were randomised.

7.1.1 Description of Included Studies

The 10 studies evaluating the LNG-IUS in the treatment of menorrhagia included 5 controlled trials and 5 case series. A summary of the controlled studies and their results is shown in Table 2, and the case series in Table 3.

Within the comparative trials, sample sizes were broadly similar for LNG-IUS and comparative treatments. The exception to this is Milsom,²² where 20 women were allocated to the LNG-IUS and 15 randomised to two crossover drug therapies. Sample size was less than 30 for each treatment arm in all but 3 studies. Two studies presented tabulated data for individual patients (Scholten 1989, Tang & Lo 1995).^{19 25} Age ranges varied considerably. Parity was reported by six studies; the proportion of parous patients in these studies was 90-100%.

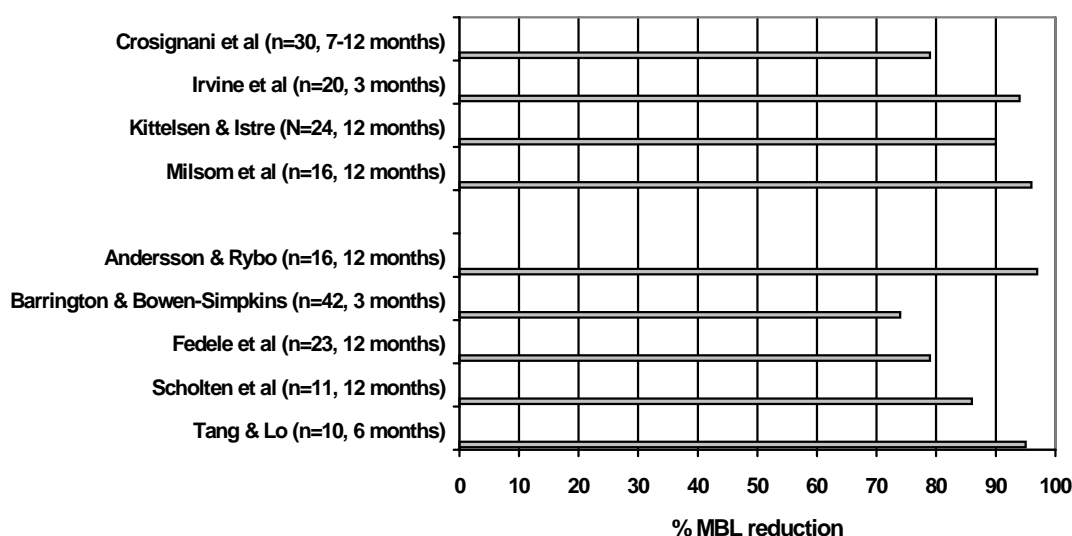
Outcome measures differed between studies, but most included menstrual blood loss (MBL), side effects plus haemoglobin and serum ferritin levels. Although MBL reduction was reported in all but one of the studies, actual blood loss was estimated by the use of a pictorial chart in three studies, rather than measured directly.^{24 51 132}

7.2 Assessment of Effectiveness

7.2.1 Effect on MBL

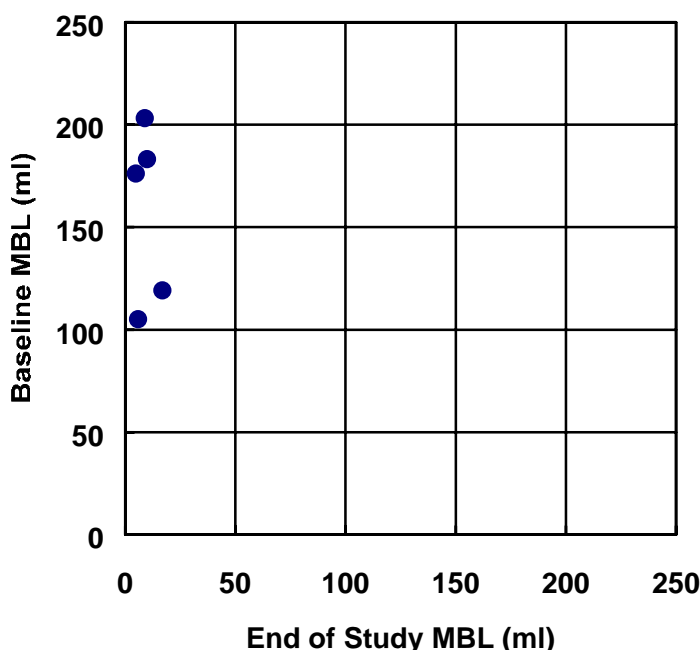
Nine of the ten studies measured MBL, and all showed statistically significant average MBL reductions over time, ranging from 74% to 97% overall. In the three controlled trials reporting MBL reduction, the range was 79% to 96%. Tables 4 (controlled trials) and 5 (case series studies) summarise in detail the MBL results, and Figure 2 shows percentage MBL reduction with the LNG-IUS for each study. All had p values <0.05 comparing base and endpoint.

Figure 2 - Percentage MBL reduction with the LNG-IUS for all studies.



Five studies measured MBL in ml, rather than by menstrual score.^{18-20 22 25} When the difference between baseline and end of study MBL is examined across the five studies reporting this outcome, wide variations are apparent. Baseline MBL ranges from 105ml (Irvine *et al*)²⁰ to 203ml (Milsom),²² while end of study MBL for women treated with LNG-IUS ranges from 5ml (Andersson & Rybo)¹⁸ to 17ml (Scholten *et al*).²⁵ End of study MBL for the LNG-IUS was considerably less than the 80ml threshold for diagnosis of confirmed menorrhagia in all studies. A scatter diagram is shown at Figure 3, demonstrating a clear, if variable difference between baseline and final MBL with LNG-IUS. Given that all differences between baseline and endpoint MBL are statistically significant, this suggests that the treatment is effective.

Figure 3 - Scatter diagram, showing MBL with the LNG-IUS at baseline against end of study MBL

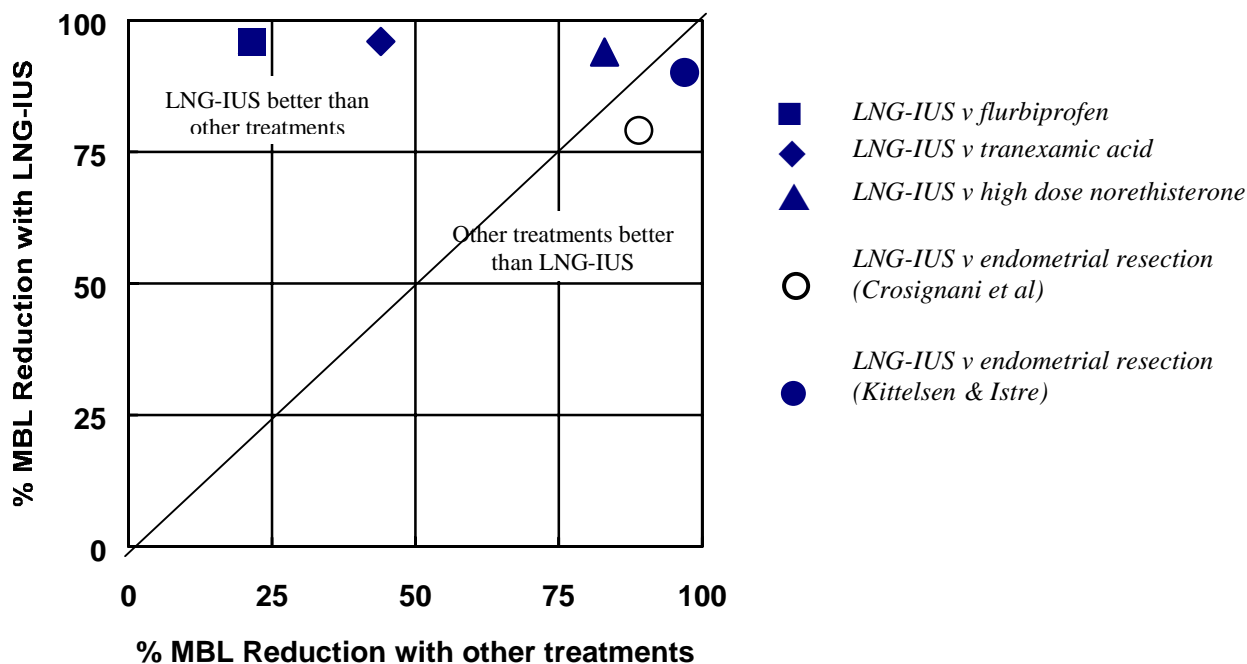


Four RCTs reported MBL reduction with LNG-IUS relative to comparator treatment. Milsom *et al* (1991)²² reported a 96% mean MBL reduction at 12 months with LNG-IUS, which was significantly greater than the 21% reduction with flurbiprofen ($p < 0.001$) and the 44% reduction with tranexamic acid ($p < 0.01$). Irvine *et al*²⁰ demonstrated a 94% median MBL reduction in the LNG-IUS group, compared with 83% reduction with high dose norethisterone at 3 months; this difference was not significant ($p = 0.56$). Crosignani *et al* (1997)⁵¹ found that the LNG-IUS was less effective than endometrial resection at 6 months, with a mean MBL reduction of 79% for LNG-IUS, compared with 89% in the endometrial resection group ($p = 0.015$). Kittelsen & Istre (1998)¹³² also found the LNG-IUS less effective than endometrial resection, with a mean MBL reduction of 90% for the LNG-IUS, compared to 98% in the endometrial resection group, though this difference was not significant.

The data from the four controlled trials with measured MBL are shown collectively in a L'Abbé plot at Figure 4, which shows the relationship between % MBL reduction for the

LNG-IUS and other treatments. It is apparent that the LNG-IUS was more effective at reducing MBL when compared with flurbiprofen and tranexamic acid; high dose norethisterone produced similar results, and the LNG-IUS performed slightly less well than endometrial resection.

Figure 4 - L'Abbé plot, showing % MBL reduction with the LNG-IUS, compared to other treatments



One query over the generalisability of results in the latter two trials^{51 132} concerns the fact that the endometrial resections were carried out in specialised academic centres, which were not representative of all hospitals, possibly resulting in better outcomes. Skills concerns are unlikely to apply similarly to the LNG-IUS, as minimal skill is required to insert the LNG-IUS (Crosignani *et al* acknowledged these issues). Longer term follow up would be desirable in general (ideally over the five year lifespan of the device), but particularly in comparison to endometrial resection which often requires further surgery within two years.²

Variations in several factors between studies precluded any valid combination of outcome data:

7.2.2 Type of study

Five of the ten studies were randomised controlled trials, with the remainder being non-comparative.

7.2.3 Interventions

The five comparative studies used various comparators.

7.2.4 Age

Ages ranged from 20 to 53. Mean age, where stated, ranged from 33 (median) to 45. Women included in three of the comparative trials (Tang & Lo 1995,¹⁹ Crosignani *et al* 1997,⁵¹ Lähteenmäki *et al* 1998²⁶) were generally older than those in other studies. Mean ages in the controlled trials were, however, broadly similar between treatment groups. None of the studies reported any association between age and any outcome measure. One study did not report ages.¹³²

7.2.5 Methods of assessing MBL reduction

Studies varied in how MBL was assessed. Methods used were the alkaline haematin method (Andersson & Rybo 1990,¹⁸ Irvine 1998,²⁰ Milsom 1991,²² Tang & Lo 1995¹⁹), modified alkaline haematin method (Scholten 1989²⁵) and pictorial MBL chart (Barrington & Bowen-Simpkins 1997,⁵ Crosignani 1997,⁵¹ Fedele 1997,²⁴ Kittelsen & Istre 1998¹³²).

7.2.6 Length of use before final MBL reporting

While six of the studies reported MBL after 12 months use, two only recorded up to 3 months, and one other recorded up to 6 months.

7.2.7 Variability in statistics used

Differing measures of central tendency were used. Median values rather than means were sometimes reported (Andersson & Rybo 1990,¹⁸ Irvine 1998,²⁰ Tang & Lo 1995¹⁹). For some studies there was insufficient information to allow calculation of standard error.

7.2.8 Variability in MBL ranges

Wide variations were reported in both baseline and end of study MBL. Irvine *et al* (1998),²⁰ for example, reported baseline ranges of 82-780ml in the LNG-IUS group and 82-336ml in the norethisterone group. End of study ranges were 0-284ml and 4-137ml respectively. Other studies show similar variability in this respect. Where both mean and median values were available, these also varied widely. In Tang & Lo (1995),¹⁹ for example, the mean baseline MBL was 247ml, compared to a median of 183ml, and mean end of study MBL was 26ml, compared to median 10ml. Differences were also observed between mean and median values in Barrington & Bowen-Simpkins (1997).⁵ One study reported standard deviations as high as 463.¹³² This variability suggests skewed data; normal distribution of data cannot be assumed.

7.2.9 Side effects

Many women included in the studies experienced side effects. Women may have experienced more than one side effect, although details of individual experiences were not always given. Eight studies with populations totalling 191 women on LNG-IUS and 116 women on comparative treatments reported side effects.

Overall, side effects for the LNG-IUS included numerous reports of intermenstrual spotting/bleeding (especially in the first three cycles), breast tenderness/pain (n=23), weight gain (16), mood swings (13), bloating (10), greasy hair (6), acne (10), depression/anxiety (3),

hair loss (2), reduced libido (2), hypertension (1), leg pain (1) and headache (1). No information on side effects was reported by Scholten (1989)²⁵ or Tang & Lo (1997).¹⁹

Irvine *et al* (1998)²⁰ asked women to record side effects in their menstrual diaries, which were completed by 12 women in the norethisterone group and 19 in the LNG-IUS group. The number of side effects reduced during the study. For norethisterone, side effects at 3 months included intermenstrual bleeding (17%), mood swings (58%), breast tenderness (17%) and periods interfering with daily life (17%). LNG-IUS patients experienced more side effects at 3 months, including intermenstrual bleeding (53%), mood swings (63%), breast tenderness (74%) and periods interfering with daily life (32%). Side effects such as headache, acne, abdominal or back pain, nausea, decreased libido, weight gain, oedema, sweating, hair loss or greasy hair were also reported, though there was no difference in their occurrence between baseline and 3 months of treatment in each group.

Milsom *et al* (1991)²² reported that 4 women treated with flurbiprofen complained of side effects including tiredness, stomach pains and nausea, but none discontinued their treatment because of these. Seven women receiving tranexamic acid reported side effects including nausea, dizziness, numbness, "restless legs", headache, and (in 3 women) vomiting and swallowing difficulties. Again, none of these patients discontinued their treatment due to side effects. Most of the women in this study treated with the LNG-IUS experienced intermenstrual bleeding or spotting, but their frequency diminished gradually.

Crosignani *et al* (1997)⁵¹ reported side effects including menopausal symptoms (2 LNG-IUS, 3 resection), recurrent menorrhagia (4 LNG-IUS, 3 resection), occasional heavy bleeding (3 LNG-IUS), spotting (12 LNG-IUS), weight gain (8 LNG-IUS, 3 resection), breast pain (6 LNG-IUS), headache (4 LNG-IUS, 3 resection), bloating (10 LNG-IUS, 2 resection), decreased libido (2 LNG-IUS, 2 resection) and pelvic pain and anxiety/depression (1 resection). Duration was not stated.

Kittelsen & Istre (1998)¹³² reported only side effects which led to discontinuation of the LNG-IUS or repeat endometrial resection.

7.2.10 Discontinuation of treatment

Studies showed varying LNG-IUS removal rates, though none were recorded in Scholten *et al* (1989)²⁵ or Tang & Lo (1995)¹⁹. Most frequent reasons overall were expulsion (n=10), intermittent intermenstrual bleeding (8), "side-effects" (3) and prolonged bleeding & spotting (3). Other reasons included severe low abdominal pain & backache, weight gain and headache, excessive bleeding, desire for hysterectomy, personal reasons and loss to follow-up.

Out of 44 patients, Irvine *et al* (1998)²⁰ recorded three discontinuations due to unacceptable drug-related side effects (2 norethisterone, 1 LNG-IUS), prolonged amenorrhoea (1 norethisterone), expulsion (1 LNG-IUS). One participant was lost to follow-up (1 norethisterone), and there was no final collection of menstrual loss data on two other participants (2 norethisterone).

Milsom *et al* (1991)²² reported discontinuations by 4 out of 20 LNG-IUS patients, due to expulsion (1), intermenstrual bleeding (2), and acne, weight gain, mood changes and intermenstrual bleeding (1). No patients receiving flurbiprofen or tranexamic acid discontinued their treatment.

Kittelsen & Istre (1998)¹³² reported discontinuations by 6 of the 30 LNG-IUS patients, due to irregular bleeding/spotting (3), pain (2), acne and greasy skin (1). Of the 29 patients receiving endometrial resection, 2 complained of pain and 2 experienced continuous bleeding problems. These 4 patients received repeat endometrial resection, though only one was carried out within the 12 month follow-up period.

7.2.11 Anaemia; haemoglobin, serum ferritin and iron levels

Haemoglobin (Hb) levels were reported in 8 studies, serum ferritin (Sf) in 6 studies (one other study recorded but did not report on Sf levels), and iron in 2 studies. Although two found no significant end of study differences from baseline in Hb and Sf levels,^{5 20} most showed marked improvements. Six studies reported improvements in Hb levels, ranging from 8-19.2%.^{18 19 22 24 25 51} The improvements in Hb levels were significant ($p < 0.05$) for each of the five studies which reported significance levels. Four studies reported increases in Sf levels, ranging from 14.5-259%,^{18 24 25 51} and these were all significant ($p < 0.005$). The two studies that included iron levels showed dramatic increases of 135.9% and 200% respectively by the end of the study^{24 51} (both $p < 0.001$).

7.2.12 Patient satisfaction, acceptability and quality of life

There were no objective measurements of health related quality of life using an acceptable disease-specific or generic score. Crosignani *et al* (1997)⁵¹ collected data using the SF36 at one year of follow up, however baseline data was not collected because the Italian version of this instrument had not been validated at the start of the study. Irvine *et al* (1998)²⁰ found that 64% of LNG-IUS users liked their treatment “well” or “very well” at 3 months, compared with 44% in the norethisterone group. 77% of the LNG-IUS patients continued with their treatment, compared with 22% on norethisterone. Significance was not stated.

Crosignani *et al* (1997)⁵¹ reported higher levels of satisfaction at 1 year than Irvine *et al*,²⁰ but satisfaction with the LNG-IUS, while high, was less than with endometrial resection – 85% were “satisfied” or “very satisfied” with the LNG-IUS, compared with 94% of the endometrial resection group. This difference was, however, not significant ($p = 0.26$). Mean differences in SF36 score at one year between treatment groups were not significant.

Barrington & Bowen-Simpkins (1997)⁵ reported that 82% of women who used the LNG-IUS were taken off the waiting list for surgery by 12 months. Lähtenmäki *et al* (1998)²⁶ reported that 64% of women cancelled surgery at 6 months, compared with 14% of women in the control group ($p < 0.001$). This might suggest that they were happier with their LNG-IUS.

Lähtenmäki *et al*²⁶ also reported that women receiving the LNG-IUS experienced a 70% reduction in an aggregated menstrual disturbance score (an aggregate of 5 variables, including general wellbeing, work performance, physical activity, sex life and leisure time activity, administered before treatment, and at 6 and 12 months thereafter or at discontinuation) ($p < 0.002$), compared with a 2% reduction in controls.

Table 2 - Overview of included controlled trials. Tabulation of Study Characteristics and Results

Study	Study Type	Selection Criteria	Trial and Size	Intervention	Mean Age (Age Range)	Prop. Parous	Outcome Measures	Duration	Drop-Out / Loss to Follow-up	Results
Crosignani <i>et al</i> (1997) ⁵¹	RCT	Women with confirmed menorrhagia, and no pelvic pathology	35 women randomised to LNG-IUS 35 women randomised to endometrial resection Size: 30 LNG-IUS 30 endometrial resection	LNG-IUS 20µg/day Endometrial resection	43.8 – IUD 45.4 – E.Res. (38-53)	100%	MBL by pictorial chart score Satisfaction with effects of treatment, at 1 year SF36 general health survey questionnaire, at 1 year Haemoglobin Serum ferritin Iron Side effects	12 months	14%	LNG-IUS group: Mean MBL reduction at 12 months 79% (p<0.001) “satisfied” or “very satisfied” 85% (p=0.26) Increase in Hb at 6 months 15.8% (p<0.001) Increase in Sf at 6 months 14.5% (p<0.001) Increase in Iron at 6 months 140% (p<0.001) Endometrial resection group: Mean MBL reduction at 12months 89% (p<0.001) “satisfied” or “very satisfied” 94% (p=0.26) Increase in Hb at 6 months 16.2% (p<0.001) Increase in Sf at 6 months 14.7% (p<0.001) Increase in Iron at 6 months 135.9% (p<0.001) No significant differences in SF36 scores between groups Side effects: 19 LNG-IUS; 9 endometrial resection
Irvine <i>et al</i> (1998) ²⁰	RCT	Women with confirmed menorrhagia, and no pelvic pathology	22 women randomised to LNG-IUS 22 women randomised to norethisterone Size: 20 LNG-IUS 16 norethisterone	LNG-IUS 20µg/day Norethisterone (5mg tds) day 5 to day 26 of cycle, for 3 cycles	38.5 – IUD (31-45) 39 – Norethisterone. (30-45)	100%	MBL Satisfaction with treatment at 3 months Decision to continue with treatment Haemoglobin Serum Ferritin Side effects	3 months	18%	LNG-IUS group: Median MBL reduction at 1 month - 85%; Median MBL reduction at 3 months - 94% (p<0.001) Liked treatment “well” or “very well” - 64% To continue – 77% Norethisterone group: Median MBL reduction at 1 month – 62%; Median MBL reduction at 3 months – 83% (p<0.001) Liked treatment “well” or “very well” - 44% To continue – 22% No significant changes in median Hb and Sf between groups Side effects: Numerous
Kittelsen & Istre (1998) ¹³²	RCT	Women with confirmed menorrhagia, and no pelvic pathology	30 women randomised to LNG-IUS 30 women randomised to endometrial resection Size: 24 LNG-IUS 29 endometrial resection	LNG-IUS 20µg/day Endometrial resection	N/S	N/S	MBL by pictorial chart score Serum ferritin Side effects	12 months (being extended to 36 months)	12%	LNG-IUS group: Mean MBL reduction at 12 months 90% (p<0.05) Endometrial resection group: Mean MBL reduction at 12months 98% (p<0.05) Sf levels not reported. Side effects: 6 LNG-IUS; 4 endometrial resection.
Lähtenmäki <i>et al</i> (1998) ²⁶	RCT	Women with no pelvic pathology, awaiting hysterectomy for confirmed menorrhagia	28 women randomised to LNG-IUS 28 women randomised to control group Size:20 LNG-IUS 26 control	LNG-IUS 20µg/day Control (continuing with current medical treatment)	42.7 – IUD 41.7 – Control (33-49)	N/S	Proportion of women cancelling decision to have hysterectomy Menstrual disturbance scores (QOL) at baseline, and 6 & 12 months Side-effects	6 months	18%	LNG-IUS group: Women cancelling hysterectomy at 6 months 64% (p<0.001) Reduction in aggregated menstrual disturbance median scores (aggregate of 5 variables) 70% (p≤0.002) Control group: Women cancelling hysterectomy at 6 months 14% (p<0.001) Reduction in aggregated menstrual disturbance median scores (aggregate of 5 variables) 2% Side-effects: 5 patients
Milsom <i>et al</i> (1991) ²²	RCT	Women with confirmed menorrhagia, and no pelvic pathology	First 20 women given LNG-IUS; next 15 randomised to drugs (cross-over design) Size: 16 LNG-IUS 15 Drugs	LNG-IUS Group: LNG-IUS 20µg/day Drugs Group: Flurbiprofen (100mg bd for 5 days) Cross-over with Tranexamic acid (1.5g tds for days 1-3, then 1g bd for days 4 & 5).	37.8 – IUD 40.5 – Drugs (31-49)	N/S	MBL Haemoglobin Side effects	12 months	11%	LNG-IUS Group: Mean MBL reduction at 3 months 82%, Mean MBL reduction at 6 months 88%, Mean MBL reduction at 12 months 96% (all p<0.001) Mean increase in Hb at 1 year 8.6% (p<0.001) Drugs Group: Flurbiprofen mean MBL reduction 21% (p<0.05), tranexamic acid mean MBL reduction 44% (p<0.01) No significant change in Hb at 1 year Side-effects: 7 tranexamic acid; 4 flurbiprofen, ‘most’ LNG-IUD patients experienced some bleeding/spotting for first three months

(N/S = not stated)

Table 3 - Overview of included case series studies.

Study	Study Type	Selection Criteria	Trial and Size	Intervention	Mean Age (Age Range)	Prop. Parous	Outcome Measures	Duration	Drop-Out / Loss to Follow-up	Results
Andersson & Rybo (1990) ¹⁸	Case Series	Women with confirmed menorrhagia, and no pelvic pathology	20 women given LNG-IUS Size: 16 LNG-IUS	LNG-IUS 20µg/day	38 (31-45)	100%	MBL Haemoglobin Serum ferritin Side effects	12 months	20%	Median MBL reduction at 3 months 86% (p<0.001) Median MBL reduction at 12 months 97% (no p value) Mean Hb increase at 12 months 8% (p<0.01) Mean Sf increase at 12 months 46.9% (p<0.001) Side effects: 3
Barrington & Bowen-Simpkins (1997) ⁵	Case Series	Women with no pelvic pathology, awaiting hysterectomy or transcervical resection of endometrium for menorrhagia, after failed trial of medical therapy	50 women given LNG-IUS Size: 42 LNG-IUS	LNG-IUS 20µg/day	39.8 (28-53)	94%	Menstrual score Haemoglobin Serum ferritin Side effects	12 months	16%	Reduction in median menstrual score at 3 months 75% (74% mean reduction) (p<0.0001) No significant change in Hb or Sf Women taken off waiting list for surgery – 82% Side effects: 3
Fedele <i>et al</i> (1997) ²⁴	Case Series	Women with adenomyosis-associated confirmed menorrhagia, and no pelvic pathology	25 women given LNG-IUS Size: 23 LNG-IUS	LNG-IUS 20µg/day	N/S (38-45)	N/S	MBL by pictorial assessment Haemoglobin Serum ferritin Iron Side-effects	12 months	8%	Mean MBL reduction at 3 months 77% (p<0.001) Mean MBL reduction at 6 months 80% (p<0.001) Mean MBL reduction at 12 months 79% (p<0.001) Increase in Hb at 1 year 19.2% (p<0.001) Increase in Sf at 1 year 259% (p<0.001) Increase in iron at 1 year 200% (p<0.001) Side effects: 23
Scholten <i>et al</i> (1989) ²⁵	Case Series	Women with confirmed menorrhagia, and no pelvic pathology	11 women given LNG-IUS Size: 11 LNG-IUS	LNG-IUS 20µg/day	33 – median (20-47)	91%	MBL Haemoglobin Serum ferritin Side effects	7-12 months	None	Mean MBL reduction at 7-12 months 86% (p<0.005) Mean increase in Hb 14.9% (p<0.05) Mean increase in Sf 35.9% p<0.005) Side effects: None
Tang & Lo (1995) ¹⁹	Case Series	Women with confirmed menorrhagia, and no pelvic pathology	10 women given LNG-IUS Size: 9 LNG-IUS	LNG-IUS (dose not stated)	45 – median (38-50)	100%	MBL Haemoglobin	6 months	10%	Median MBL reduction at 1 month 54% (p=0.004) Median MBL reduction at 3 months 87% (p=0.031) Median MBL reduction at 6 months 95% (p=0.008) 19.2% Mean increase in Hb at 6 months Side effects: None

(N/S = not stated)

Table 4 - Summary of MBL results (controlled trials)

Study	n	Baseline MBL (ml)	End of study MBL (ml)	MBL difference (ml)	% MBL reduction	End point
Crosignani <i>et al</i> (1997) ⁵¹	30	<u>LNG-IUS:</u> mean 184.8 SD 62.2	mean 38.8 SD 37.1	146 (CI 123-169)	79% *	12 months
	30	<u>Endometrial Resection:</u> mean 203.2 SD 77.4	mean 23.5 SD 32.6	180 (CI 152-208)	89% *	
Irvine <i>et al</i> (1998) ²⁰	20	<u>LNG-IUS:</u> median 105 range 82-780	median 6 range 0-284	99 z=12.5	94% *	3 months
	16	<u>Norethisterone:</u> median 120 range 82-336	median 20 range 4-137	100 z=8.23	83% *	
Kittelsen & Istre (1998) ¹³²	24	<u>LNG-IUS:</u> mean 418 SD 349	mean 42 SD 99.7	376	90% ‡	12 months
	29	<u>Endometrial Resection:</u> mean 378 SD 463	mean 6.6 SD 15	371.4	98% ‡	
Milsom <i>et al</i> (1991) ²²	16	<u>LNG-IUS:</u> mean 203 range 80-381 SEM ±25.2	mean 9 range 0-33 SEM ±2.7	194	96% *	12 months
	15	<u>Flurbiprofen:</u> mean 295 range 81-701 SEM ±52	mean 223 range 50-636 SEM ±44	72	21% ‡	
	15	<u>Tranexamic Acid:</u> mean 295 range 81-701 SEM ±52	mean 155 range 36-511 SEM ±33	140	44% §	

Table 5 - Summary of MBL results (case series)

Study	n	Baseline MBL (ml)	End of study MBL (ml)	MBL difference (ml)	% MBL reduction	End point
Andersson & Rybo (1990) ¹⁸	16	median 176 range 80-381	median 5 range 0-33	171	97% *	12 months
Barrington & Bowen-Simpkins (1997) ⁵	42	mean 120 median 85 SD 98	mean 31 median 21 SD 28	89	mean 74% * median 75%	3 months
Fedele <i>et al</i> (1997) ²⁴	23	mean 211 SD 61	mean 44 SD 18	167	79% *	12 months
Scholten <i>et al</i> (1989) ²⁵	11	mean 119 SD 72	mean 17 SD 14	102	86% §	7-12 months
Tang & Lo (1995) ¹⁹	10	mean 247 median 183 (range 82-563) SD 158.1 SE 52.7	mean 26 median 10 (range 0-143) SD 45.6 SE 15.2	mean 221 median 173	mean 89% median 95% §	6 months

Key: ‡ p<0.05 § p<0.01 * p<0.001

7.3 Economic Analysis

No economic studies evaluating the LNG-IUS were identified. As detailed in 8.2.5 above, there was insufficient information on quality of life to permit a cost utility analysis. Cost estimates of the alternative treatments derived below, and information on effectiveness from the primary studies are combined to give an estimate of cost-effectiveness.

7.3.1 Costs

The cost of the LNG-IUS is around £99. Its expected duration of use is five years, equating to just under £20 per year. This makes it over ten times more expensive than other IUDs available in the UK.^{6,94} Other resource use involved for the LNG-IUS varies between primary and secondary care, and includes insertion, follow-up visits, removal and counselling.⁶³ As a contraceptive device, schedule fees are set for insertion and follow-up visits. In the absence of other cost data on the LNG-IUS, we use these set fees to provide an indication of overall cost of the intervention. For primary care, insertion fees are £54.70,¹²⁸ with follow-up visits at £16.40 for subsequent years.¹²⁸ It should be noted that not all GPs are licensed to provide contraceptive services. For secondary care, the insertion cost averages £77, with follow-up visits at £52.¹²⁹ With one visit for insertion in year one and one follow-up visit in each subsequent year, an estimate of costs over five years for LNG-IUS is £219 in primary care and £384 in secondary care (undiscounted).

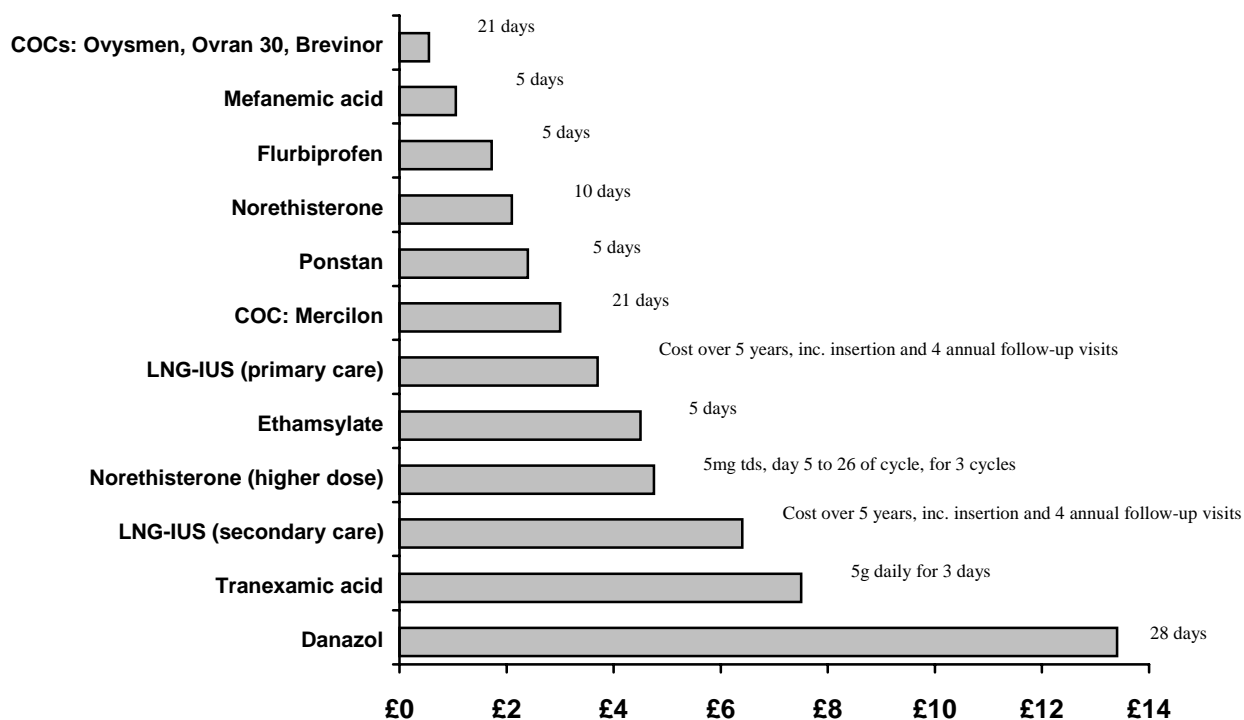
This is a rough estimate, and further costs may need to be considered. It is difficult to attach accurate and consistent costs to removal and counselling, as clinicians may spend varying amounts of time on these activities, and GPs especially may not consider them additional to a normal patient consultation. Furthermore, counselling may equally apply to other medical treatments (for example, to explain possible side effects) or surgery. There may be economic concerns around the early discontinuation of the device due to pelvic pain, pelvic inflammatory disease or desire to become pregnant. The above cost estimates do not include these effects or the costs associated with adverse events.

7.3.2 Cost effectiveness

a. Comparison with drugs

The monthly costs of primary care medical treatments compare as follows:

Figure 5 - Costs of drug treatment at usual dose for one menstrual cycle, based on treatment for number of days stated



(adapted from Scott 1999)⁶⁰

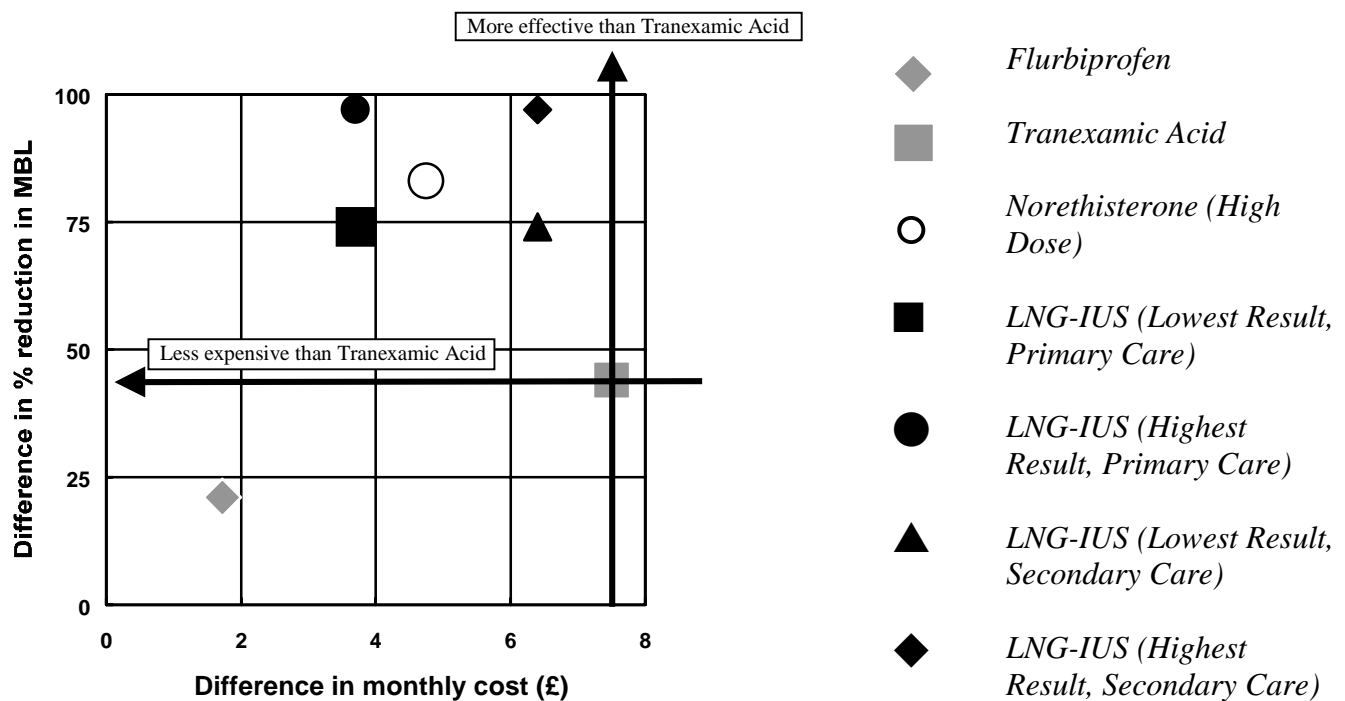
It should be noted that while costings have been calculated for monthly doses, it is not always appropriate to take these drugs on an ongoing basis. Patients taking tranexamic acid or mefenamic acid, for example, should normally be reviewed at three months.

The almost twofold increase in the cost of LNG-IUS in secondary care is explained by higher hospital outpatient costs. Thus, the LNG-IUS provided in primary care proved cheaper than tranexamic acid or norethisterone at the higher dose and duration. When provided in secondary care, the LNG-IUS is more expensive than high dose norethisterone but still cheaper than tranexamic acid. The LNG-IUS proved more effective in MBL reduction than either high dose norethisterone or tranexamic acid. Flurbiprofen, while cheaper, proved less effective at reducing MBL than any comparative treatment in the included studies.

A cost effectiveness plane is shown at Figure 6, illustrating how the different treatments compare. This demonstrates that the LNG-IUS in primary care is less costly and more effective than tranexamic acid, which is considered the most effective and acceptable drug treatment for menorrhagia.^{2 11 58 59} The LNG-IUS in primary care (both lowest and highest recorded effectiveness) appears in the upper left quadrant, representing higher effectiveness with lower cost. Although norethisterone at normal doses is considered ineffective for the treatment of menorrhagia,^{1 2 9 10 11 56 58} at high doses, this drug has been shown to be very

effective,²⁰ although more expensive than the LNG-IUS in primary care. The LNG-IUS in secondary care (both lowest and highest recorded effectiveness) also appears in this quadrant, though is more expensive than high dose norethisterone. Flurbiprofen appears in the lower left quadrant, representing lower effectiveness with lower cost. No treatments appear in the upper right quadrant, representing higher effectiveness with higher cost, or in the lower right quadrant, representing lower effectiveness with higher cost. When compared with tranexamic acid, the other treatments are therefore cheaper and more effective, with the exception of Flurbiprofen. It should be borne in mind that all these estimates come from small studies and are therefore relatively imprecise.

Figure 6 - Cost Effectiveness Plane for drug therapies, comparing difference in monthly drug costs and % MBL reduction with Tranexamic Acid



Inability to combine MBL data prevents a pooled estimate of the cost effectiveness of LNG-IUS compared to other medical treatments. Cost-effectiveness can be estimated separately for LNG-IUS compared to each of the alternative medical treatments used in the two RCTs reporting MBL reduction.^{20 22} However, this would give results in terms of cost per percentage point MBL reduction, which is an outcome measure of little meaning. Such an outcome measure also ignores adverse events and the broader impact on health related quality of life.

The LNG-IUS dominates the most common drug treatment, Tranexamic Acid. As shown in Figure 6, LNG-IUS is both more effective and less expensive than Tranexamic Acid.

From the data presented above, LNG-IUS and high dose norethisterone appear to be equivalent treatments for menorrhagia in women, in terms of both effectiveness and cost. Irvine *et al* found no significant difference in the effectiveness of these treatment

alternatives.²⁰ Monthly cost data show norethisterone to lie between the ends of the predicted cost range of LNG-IUS.

LNG-IUS is far more effective than flurbiprofen in reducing MBL. It is, however, more expensive. Using trial data (Milsom *et al* 1991),²² and cost estimates above, LNG-IUS costs an additional £3.25-£7.67 per percentage point MBL reduction. Such an outcome measure has little meaning. However, we would argue that such a comparison has equally little meaning as Flurbiprofen is not seen as a realistic treatment alternative, as suggested by its effectiveness (reducing MBL by less than one quarter from baseline levels).

b. Comparison with surgery

The appropriate comparison with the LNG-IUS is probably with other drugs. How the LNG-IUS might be compared with surgical interventions is discussed below. It is extremely difficult to compare the cost-effectiveness of surgery with the LNG-IUS, as it would require complex models beyond the scope of this report. Hysterectomy produces complete cessation of menstrual blood loss. Costs are normally therefore limited to a few outpatient clinic or GP attendances, in-patient hotel costs, drugs and the procedure itself. Endometrial resection is around half the cost of hysterectomy, though it may need to be repeated and patients may eventually have a hysterectomy.

The LNG-IUS however, needs to be prescribed every five years if used on an ongoing basis. It may be discontinued when the patient becomes menopausal, or its use may be continued for HRT.¹⁰⁹⁻¹¹¹ It is therefore difficult to estimate its average length of use, particularly because of limited experience, following its licensing only 4 years ago. Further studies will therefore be necessary to examine this in detail, preferably in a large sample of women.

The effectiveness of LNG-IUS compared to endometrial resection has been assessed in two RCTs. Crosignani *et al* found endometrial resection to be significantly more effective than LNG-IUS.^{51 132} However, Kittelsen & Istre found the small difference between treatments, though positive, to be non-significant.¹³²

Given the concerns noted above on cost comparisons, and the lack of significant difference in one trial in addition to the concerns over the meaning of outcome measures of % MBL reduction, further assessment of the cost-effectiveness of LNG-IUS compared to surgery is not attempted here.

Although quantitative calculations are not practical, it is likely that the cost per QALY is at the cheap end of the scale for the LNG-IUS, endometrial resection and tranexamic acid. All are reasonable options, depending on patient preference.

In a study comparing the LNG-IUS to endometrial resection, Crosignani *et al* (1997)⁵¹ reported higher patient satisfaction in the endometrial resection group, though this difference was not significant.

Sculpher⁴⁷ has shown that women receiving endometrial resection experienced a significantly higher increase in the value they attached to their health state 2 weeks after the procedure, compared with hysterectomy, although this had disappeared at 4 months. Measurement of change in health state valuation was carried out using the EuroQol visual analogue scale. Use of the scale involved asking patients to retrospectively value their health state before, immediately after and 4 months after surgery. Further follow-up data has now been

published.¹³³ At a mean overall follow-up of 2.2 years, women initially randomised to abdominal hysterectomy were doing as well or better on both EuroQol and SF36 measures of outcome than women randomised to endometrial resection. Unfortunately the EuroQol has not yet been applied to LNG-IUS users, ruling out comparison at this time. SF36 data is currently not available to show impact on quality of life of LNG-IUS.⁵¹ One ongoing trial will collect comparative quality of life data on LNG-IUS and surgical treatment alternatives, which will enable an assessment of the cost-utility of LNG-IUS compared to endometrial resection.

The available evidence suggests that the use of the LNG-IUS is likely to reduce waiting lists for surgery.

8 Conclusions

The included studies (both RCTs and case series) show that use of the LNG-IUS can significantly reduce menstrual blood loss in women with confirmed menorrhagia. Although variations within and between the studies meant that percentage MBL reductions could not be combined in meta-analysis, each reported a statistically significant difference between baseline and final MBL with the LNG-IUS, ranging from 74% to 97% overall.

The LNG-IUS has proved more effective at reducing MBL than either tranexamic acid (considered the most effective drug therapy) ($p < 0.01$) or flurbiprofen ($p < 0.001$) in the studies included in this review. High dose norethisterone is shown to have a similar effect to LNG-IUS (difference not significant – $p = 0.56$).

While patient satisfaction and quality of life were greater with the LNG-IUS when compared to drug treatments, its efficacy was slightly inferior to endometrial resection in two studies (statistically significantly so in one study).

Two studies showed that a large proportion of patients on the waiting list for surgery for menorrhagia cancelled their operations after receiving the LNG-IUS. This has implications for hospital waiting lists for hysterectomy and endometrial resection.

In the primary care setting, the LNG-IUS is also cheaper per cycle than several medical alternatives, making it a treatment that should be considered for suitable women. Its use may be especially cost-effective in primary care, although not all GPs provide contraceptive services, and those who do may need some additional training in insertion technique.

To allow more reliable conclusions to be drawn, further research comparing the LNG-IUS to other treatments for menorrhagia is indicated. This should ideally include larger numbers of randomly selected patients, involve several centres and patient follow-up for at least 2 years, and use generic outcome measures such as SF36, SF12 or EQ-5D, so that existing outcome data can be compared to data on surgery. The manufacturers of the LNG-IUS have confirmed that further trials are underway, in preparation for their UK license application for its use in the treatment of menorrhagia and hormone replacement therapy. No results are expected in the near future, however. One of the trials reported here¹³² will provide follow-up data to three years on the relative effectiveness of LNG-IUS and endometrial resection in the near future.

9 Summary

The LNG-IUS is cheaper and more effective than current medical therapy for women with menorrhagia. The device can be used by women who have no pelvic pathology, who desire contraception, have no contra-indications to the device and are preferably parous. Unlike surgery, the contraceptive effect of the LNG-IUS is reversible, preserving long term fertility.

Under these circumstances, the LNG-IUS provides an efficacious, satisfactory and cost-effective choice in the treatment of menorrhagia compared to drug therapies, and may reduce demand for surgical treatment. Precise effectiveness relative to other treatments can only be established in larger RCTs.

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