The effectiveness of the Mirena coil (levonorgestrel-releasing intrauterine system) in menorrhagia


Authors' objectives
The authors state the following review question: 'Does the use of levonorgestrel-releasing intrauterine system (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?'

Searching
The following sources were searched during October and November 1998 (with an update search in March 1999): MEDLINE, CINAHL, EMBASE, Grateful Med, DARE, NHS EED, HTA, the Cochrane Library, Best Evidence, the archive facility on the BMJ Website, the Internet, and the reference lists in review articles. The MeSH terms and textwords used were 'menorrhagia', 'IUD', 'hysterectomy', 'levonorgestrel', 'progestin' and 'Mirena'.

Appropriate references were also obtained from Schering Health Care Ltd. (the manufacturers of LNG-IUS), the Royal College of Obstetricians and Gynaecologists Audit Unit, handsearches of literature available locally (Journal of Family Planning Diplomate), colleagues (published and unpublished data), and subject experts. Articles reported in any language were considered.

This review has also been published as a separate article (see Other Publications of Related Interest).

Study selection
Study designs of evaluations included in the review
All study designs were included, but emphasis was given to controlled clinical trials. The duration of follow-up in the included studies ranged from 3 to 12 months.

Specific interventions included in the review
Studies were included if the interventions were LNG-IUS (20 microg/day) alone, or versus placebo or any medical or surgical therapy, or no treatment for menorrhagia. Only studies using the current version of the hormonal intra-uterine device (IUD) were included, as previous versions (which are no longer available in the UK) using different doses of levonorgestrel produced different results.

Participants included in the review
Studies were included if the participants were women with heavy menstrual blood loss (equal to or greater than 80 mL/cycle). Studies were excluded if they were not carried out on women with confirmed menorrhagia. They were also excluded if they included women with postmenopausal bleeding more than one year from their last period, women with contraindications to LNG-IUS, or LNG-IUS devices releasing doses other than 20 microg/day. The study populations included women with confirmed menorrhagia in primary care, secondary care or family planning settings. The age of the participants in the included studies, where reported, ranged from 20 to 53 years.

Outcomes assessed in the review
Studies were included only if they had outcome information on menstrual blood loss (MBL). Ideally, there would also be information on patient satisfaction and acceptability, quality of life and the cost-effectiveness.

The outcomes measured by the included studies differed, but most included MBL, side-effects, plus haemoglobin and serum ferritin levels. While the reduction in MBL was reported in all but one of the studies, the actual blood loss was estimated using a pictorial chart in three studies, rather than by direct measurement. The methods used to assess MBL were the alkaline haematin method, modified alkaline haematin method, and pictorial MBL chart.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

**Assessment of study quality**

Information relating to the quality of included studies was collected. This including whether the participants were randomised to the treatment groups; whether the randomisation method was specified; whether the inclusion criteria were specified; whether there was clear definition of the patient groups; whether intention to treat analysis was used; and whether the loss to follow-up was reported. Two independent reviewers assessed the quality of the studies, and any differences were resolved by discussion.

**Data extraction**

A checklist was used to collect data on each included study. This covered study design, setting, intervention, whether menorrhagia was confirmed in the participants, and the outcome measure reported. Two independent reviewers extracted the data, and any differences were resolved by discussion.

**Methods of synthesis**

How were the studies combined?
The results were presented as a narrative summary. The results of the individual primary studies were summarised according to the outcome measure in tabular format and in the text. In addition, the results of RCTs (in terms of MBL reduction) were presented graphically.

How were differences between studies investigated?
The authors do not state a method for assessing any differences between the studies.

**Results of the review**

Ten studies fulfilled all the inclusion criteria and were included in the review: 5 randomised controlled trials (RCTs) and 5 case series. The included studies involved a total of 381 participants (265 in the RCTs and 116 in the case series).

Nine of the 10 included studies measured MBL; all showed statistically-significant mean MBL reductions, ranging from 74 to 96% (P<0.05 in all cases). Four studies reported a reduction in MBL with LNG-IUS relative to a comparator treatment. The MBL reduction with LNG-IUS (96%) was significantly greater than that achieved with flurbiprofen (21%), (P<0.001), or tranexamic acid (44%), (P<0.01). However, it was not significantly different from that achieved with norethisterone (P=0.56). Two studies measuring MBL reduction compared LNG-IUS with endometrial resection. One found no significant difference, while the other found that LNG-IUS was less effective than endometrial resection (P=0.015); the reduction in MBL was 79% with LNG-IUS versus 89% with endometrial resection.

Haemoglobin levels were reported in 8 studies, serum ferritin in 6 studies, and iron in 2 studies. Five studies reported statistically-significant improvements in haemoglobin levels (P<0.05), while 4 studies reported statistically-significant increases in serum ferritin (P<0.005). Both studies that reported iron levels showed significant increases (P<0.001).

Eight studies with populations totalling 191 participants on LNG-IUS reported side-effects, versus 116 participants on comparative treatments. The side-effects for LNG-IUS included intermenstrual spotting or bleeding (numerous reports), breast tenderness or pain (n=23), weight gain (n=16), mood swings (n=13), bloating (n=10), greasy hair (n=6), acne (n=10), depression or anxiety (n=3), hair loss (n=2), reduced libido (n=2), hypertension (n=1), leg pain (n=1) and headache (n=1).

There were no objective measurements of health-related quality of life using an acceptable disease-specific or generic score.

**Cost information**
No economic studies evaluating LNG-IUS were identified. There was insufficient information on quality of life to permit a cost-utility analysis.

The cost of the LNG-IUS is around £99, equating to just under 20 per year with a duration of use of 5 years. When the insertion and annual follow-up costs are taken into account, the LNG-IUS costs £219 in primary care and £384 in secondary care. These estimates do not include the costs associated with early discontinuation or with adverse events.

The LNG-IUS provided in primary care proved to be cheaper than tranexamic acid or higher dose norethisterone. 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 LNG-IUS would require complex models. The available evidence suggests that the use of LNG-IUS is likely to reduce surgical waiting lists.

**Authors' conclusions**
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 contraindications 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 in comparison with drug therapies. In addition, it may reduce demand for surgical treatment. The precise effectiveness relative to other treatments can only be established in larger RCTs.

**CRD commentary**
The review question was clear and well-defined in terms of the inclusion and exclusion criteria. There is some ambiguity relating to the inclusion criteria, which specify that studies must provide outcome data on MBL; one of the ten included studies did not measure MBL. The search strategy appeared comprehensive, although the time periods covered were unclear (no start dates were reported), and no inappropriate restrictions were applied.

No formal validated method of quality scoring was reported. The authors used a checklist that contained elements known to relate to methodological bias. The data extracted using this checklist was reported in the review, but was not used to either exclude studies or to give differential weight to the included studies. The potential impact of methodological flaws in the primary studies upon the findings of this review should, therefore, be considered.

The details of the individual primary studies were generally well reported. It is notable that the included studies covered differing age groups and, although the details were not reported, the authors highlighted between-study differences in the baseline MBL; these are likely to represent differences in the baseline severity of the disease. These population differences, along with methodological variations between the studies, cast doubt upon the generalisability of results in the wider population.

The results of the primary studies were clearly summarised and important methodological issues were highlighted. However, the authors' positive conclusions, with respect to the effectiveness of LNG-IUS in comparison with other medical treatments, are difficult to justify given that they appear to be based upon the findings of only one very small study. The general positive conclusions in favour of the LNG-IUS seem ambitious in the light of the limited evidence available and the reported side-effect profile of these devices.

**Implications of the review for practice and research**
Practice: The authors state that the West Midlands Development and Evaluation Committee would have 'supported' this intervention on the basis of the cost-effectiveness analysis 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.

Research: The authors state that to allow more reliable conclusions to be drawn, further research comparing 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 two years, and use generic outcome measures (e.g. SF36, SF12 or EQ-5D) so that existing outcome data can be compared with 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. One of the trials included in this review will provide follow-up data to three years on the relative effectiveness of LNG-IUS and endometrial resection.

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**Bibliographic details**

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**Other publications of related interest**

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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.