A randomised controlled trial of the clinical effectiveness and cost-effectiveness of the levonorgestrel-releasing intrauterine system in primary care against standard treatment for menorrhagia: the ECLIPSE trial

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Declared competing interests of authors: Janesh K Gupta reports personal fees and non-financial support from training workshops for Ethicon, personal fees and non-financial support from Bayer, outside the submitted work. Joe Kai reports personal fees from Bayer Group for a postgraduate lecture outside the submitted work.

Published October 2015
DOI: 10.3310/hta19880

Scientific summary

Levonorgestrel for menorrhagia: the ECLIPSE trial

Health Technology Assessment 2015; Vol. 19: No. 88
DOI: 10.3310/hta19880

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Heavy menstrual bleeding (HMB), also called menorrhagia, is a common problem that can significantly affect women's lives, burdening individuals and health-care systems. Initial management should usually be medical, using tranexamic acid or mefenamic acid, combined oral contraceptives or the levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena®, Bayer). Short-term reduction in menstrual blood loss may not translate into an improvement in a woman's overall menstrual experience or quality of life (QoL) or her need to seek further treatment, particularly as LNG-IUS discontinuation rates can be high.

Objectives

Primary objective

To assess the clinical effectiveness of the LNG-IUS compared with usual medical treatment for women seeking treatment for HMB in primary care in the short term (2 years following randomisation).

Secondary objective

- To assess the clinical effectiveness of initial treatment with the LNG-IUS compared with usual medical treatment for women seeking treatment for HMB in primary care in the medium term (5 years following randomisation).
- To determine the cost-effectiveness of the LNG-IUS compared with usual medical treatment in the short and medium term.
- To explore the perspectives of trial participants or women with HMB who declined to be randomised in a longitudinal qualitative study.
- To measure the reliability and validity properties of the Menorrhagia Multi-Attribute Scale (MMAS).

Methods

Study randomised trial

Women between 25 and 50 years who presented to their general practitioner (GP) with HMB over at least three consecutive cycles were eligible to participate. Women were excluded if they intended to become pregnant over the next 5 years, were taking hormone replacement therapy or tamoxifen (Soltamox™, Rosemount Pharmaceuticals), had intermenstrual or post-coital bleeding or findings suggestive of fibroids or other disorders, or had contraindications to, or a preference for, either the LNG-IUS or usual medical treatments. All patients provided written informed consent.

Patients were allocated to a treatment group in a 1 : 1 ratio via a central randomisation service, with minimisation used to achieve balance between the groups with respect to age (< 35 years or ≥ 35 years), body mass index (≤ 25 kg/m^2 or > 25 kg/m^2), duration of symptoms (< 1 year or ≥ 1 year), need for contraception and presence or absence of menstrual pain.

Participants were randomly assigned to either the LNG-IUS or usual medical treatment. Usual treatment options included mefenamic acid, tranexamic acid, norethisterone, a combined oestrogen–progestogen or progesterone-only oral contraceptive pill (any formulation), or medroxyprogesterone acetate (Depo-Provera™, Pfizer Ltd) injection and were chosen by the physician and patient on the basis of contraceptive needs or the desire to avoid hormonal treatment.

The primary outcome measure was the condition-specific MMAS, which is designed to measure the effect of HMB on six domains of daily life (practical difficulties, social life, psychological health, physical health, work and daily routine, and family life and relationships).

Secondary outcome measures included general health-related QoL [using the Short Form questionnaire-36 items (SF-36) and the European Quality of Life-5 Dimensions (EQ-5D)] and sexual activity. Outcomes were obtained before randomisation and at 6 months, 1, 2 and 5 years after randomisation. Data were collected regarding all serious adverse events, hospitalisations and reasons for discontinuation of the study drug.

The study was designed for 90% power (at $p < 0.05$) to detect small to moderate (0.3 standard deviations) differences in the mean MMAS score between groups at any one time point. This required an enrolment of 470 patients; we increased the sample size to 570 to allow for up to 20% loss to follow-up.

Analysis was by intention to treat with continuous measures compared using multilevel repeated-measures models, including parameters allowing for participant, treatment, time and baseline score. A range of sensitivity analyses was performed on the primary outcome to test the robustness of the results.

Longitudinal qualitative study

A purposeful sample of women randomised into the ECLIPSE (clinical effectiveness and cost-effectiveness of levonorgestrel-releasing intrauterine system in primary care against standard treatment) trial for menorrhagia, or who declined participation owing to strong preferences for a particular treatment, was selected. Fifty-one semistructured face-to-face interviews were conducted in the respondents' homes by a female researcher.

Initial interviews were conducted within 1–3 months of commencing medical treatments and between 12 and 14 months later. Interviews followed broad topic areas including menstrual history and experience, social factors influencing experience, relationships and family life, and emotional well-being as well as treatment preference and experience of treatments. Interviews were transcribed verbatim. Data were analysed using iterative constant comparison to identify emerging themes until saturation and respondent validation.

Economic evaluation

A state transition model-based cost–utility analysis was undertaken alongside the randomised trial. The model structure was informed by clinical input and the pathways followed by women in the trial, and all parameters used were based on trial data.

The evaluation was based on an outcome of cost per quality-adjusted life-year (QALY), derived from the EQ-5D and SF-36 values [using a Short Form questionnaire-6 Dimensions (SF-6D) conversion algorithm], obtained up to 5 years. Costs were collected from a UK NHS perspective in a primary care setting, with data on health-care resource use collected from women. Two analyses based on 2- and 5-year time horizons were conducted.

The intention-to-treat analyses were reported, in terms of incremental cost-effectiveness ratios (ICERs), as cost per QALY gained. The base-case analysis and three deterministic sensitivity analyses were carried out using the EQ-5D and then repeated using the SF-36 as an additional sensitivity analysis. Uncertainty in the model was explored by conducting both deterministic and probabilistic sensitivity analysis (PSA); the latter used to construct cost-effectiveness acceptability curves.

Results

Clinical effectiveness

Between February 2005 and July 2009, a total of 571 women with HMB from 63 UK centres were randomly assigned to either the LNG-IUS (285 women) or usual medical treatment (286 women). In the usual medical treatment group, 75% were initially treated with mefenamic acid or tranexamic acid or a combination of these two drugs. Study questionnaire booklets were returned by 84% and 74% of the participants at 2 and 5 years, respectively.

Women in the LNG-IUS group were almost twice as likely as those in the usual treatment group to still be receiving their assigned treatment at 2 years (64% vs. 38%; $p < 0.001$), while by 5 years only 47% had a LNG-IUS in place and 15% were still taking usual medical treatment. The most common reasons cited for discontinuation of the LNG-IUS were lack of effectiveness and irregular or prolonged bleeding. Of the 228 women who discontinued usual medical treatment by 5 years, 43% switched to the LNG-IUS. The most common reason for discontinuation of usual medical therapy was lack of effectiveness.

At 6 months, total scores on the MMAS had improved significantly, compared with baseline scores, and these improvements were maintained through to 2 years. Improvements in these scores were significantly greater among women assigned to the LNG-IUS than among those assigned to usual treatment over the course of 2 years [mean difference in scores 13.4 points, 95% confidence interval (CI) 9.9 to 16.9 points; $p < 0.001$]. However, this difference between groups was reduced and no longer significant by 5 years (mean difference in scores 3.9 points, 95% CI –0.6 to 8.3 points; $p = 0.09$).

In a sensitivity analysis that excluded women who crossed over from the assigned treatment to the other study treatments, improvement with the LNG-IUS compared with usual medical treatment increased (mean difference in scores over 2 years was 17.8 points, 95% CI 14.1 to 21.5 points; $p < 0.001$). Other sensitivity analyses yielded results that were not materially different from the results of the primary analysis.

Domains from the SF-36 were generally significantly improved from baseline in both groups at all time points up to 2 years, although the scores were better for women in the LNG-IUS group than for those in the usual treatment group in seven of the eight domains in the analysis over all time points; mental health was the only domain for which there were no significant between-group differences. By 5 years, the only significant difference between groups was seen in the general health perception domain of the SF-36 and favoured the LNG-IUS. No significant differences were seen between treatments with respect to the EQ-5D instrument. The treatments did not differ significantly with respect to the scores for the pleasure, discomfort and frequency domains of the Sexual Activity Questionnaire in either the short or medium term. There were no significant differences in serious adverse events between groups.

Five-year surgery-free survival rates were comparable, irrespective of initial treatments, estimated to be 80% (95% CI 74% to 84%) in the LNG-IUS group versus 77% (95% CI 71% to 82%) in the usual medical treatment group (hazard ratio 0.90, 95% CI 0.62 to 1.31; $p = 0.6$). In total, there were 24 ablations in the LNG-IUS group versus 31 in the usual treatment group, as well as 30 hysterectomies in both groups.

Economic evaluation

Using the EQ-5D, at 2 years, the relative cost-effectiveness of the LNG-IUS compared with usual medical treatment was £1600 per QALY, which by 5 years was reduced to £114 per QALY in the base-case analyses. This increase in cost-effectiveness is caused by both an increase in the mean difference in QALYs generated (of 0.023) between 2 and 5 years and a reduction in the mean difference in the costs of treatment over the same period, from a difference of £100 at 2 years to a difference of £17 at 5 years. All deterministic sensitivity analyses supported the base-case results. PSAs showed that from £2000 per QALY at 2 years, and £500 at 5 years, the LNG-IUS has a greater probability of being the more cost-effective intervention.

However, using the SF-36 to produce utility values, usual medical treatment was assessed as being less costly, by £100, and generated 0.002 more QALYs than the LNG-IUS at both 2 and 5 years, showing that usual medical treatment dominates treatment using the LNG-IUS.

Longitudinal qualitative study

The findings show that women's experiences and expectations of medical treatments for HMB vary considerably and change over time. Practitioners, in addition to considering a range of practical issues when discussing treatments with women, should consider that rate of menstrual blood flow, pain and well-being, alongside wider functioning socially or at work, may be as or more important to women as volume of menstrual blood loss experienced. Women had high expectations of a prompt effect from medical treatments. Unpredictable irregular bleeding with the LNG-IUS was more problematic than the volume of blood loss for women in this study, owing to its impact on their established behavioural coping mechanisms for HMB. Women viewed standard treatment options, such as oral tranexamic acid, as a short-term measure, and one that was more within their personal control.

Conclusions

The results of the ECLIPSE trial show that the LNG-IUS, compared with usual medical therapies, leads to greater improvement over 2 years in women's assessments of the effect of HMB on their daily routine, including work, social and family life, and psychological and physical well-being. These findings were no longer significantly different at 5 years.

The higher rate of discontinuation in the usual treatment group than in the LNG-IUS group could reflect greater symptom relief with the LNG-IUS, but another possible explanation is that discontinuation of usual medical treatment does not require consultation. Nonetheless, by 5 years, 53% of women in the LNG-IUS group had had the system removed, generally owing to lack of effectiveness or to irregular or prolonged bleeding.

In the primary care setting, treating HMB using the LNG-IUS costs more, but is also more effective, using the EQ-5D as the outcome, than usual medical treatment in both the short and medium term. As the National Institute for Health and Care Excellence (NICE) guidelines recommend interventions if the ICER is below £20,000 per QALY, the LNG-IUS would be considered cost-effective. The difference in the cost-effectiveness results derived by using the alternative measures to value QoL will have a considerable impact on cost-effectiveness decisions. The different measures did not just change the strength of cost-effectiveness of the same treatment, but the most cost-effective treatment itself changed.

Implications for health care

The results provide unique and valuable practical information for women and primary care practitioners when considering choice of, and what to expect from, medical treatments for HMB. Our clinical results support the NICE guidelines that recommend that medical treatment options should be considered when women initially present with HMB in primary care and that the LNG-IUS should be considered first. Women with HMB, a relatively normal-sized uterus on examination and no other risk factors (e.g. intermenstrual bleeding, post-coital bleeding, irregularity of the menstrual cycle which has been assessed by an endometrial biopsy) can be successfully treated and expect a significant reduction in the range of negative impacts of HMB on QoL. Although the LNG-IUS is more effective than other usual medical options within the first 2 years of treatment, both the LNG-IUS and usual medical treatments are shown to be helpful initial choices 5 years later. The low overall rates of surgery underline the importance and feasibility of initial medical management of women with HMB in primary care, and the avoidance of referral to secondary care.

The use of the LNG-IUS is cost-effective in both the short and medium term, using the method generally recommended by NICE. However, when the SF-6D is used to generate QALYs, the main base-case results are reversed and usual medical treatment is shown to be more cost-effective at both 2- and 5-year time points. Therefore, the recommendation to decision-makers differs depending on the outcome measure used.

Qualitative data indicate that clinicians in primary care should also focus on the wider life context for those presenting with HMB rather than solely on the amount of blood loss experienced by women. They support the trial evidence that if women persevere with their LNG-IUS, they will probably experience significant improvement in menstrual symptoms and related QoL. Our data suggest other treatment options, while less effective, may suit individual circumstances by remaining helpful and more within their control.

Recommendations for further research

It will be important to continue assessment of the ECLIPSE trial participants to 10 years, as we expect that over half of our cohort will have reached menopause at that stage. This can examine the clinical and health-service trajectories that women initially treated for HMB in primary care may follow in the longer term. Relevant data are lacking in these contexts. Such further research may helpfully identify the nature of continuing use of treatments, particularly the LNG-IUS, and any differential impact on frequency of surgical interventions in the longer term.

The difference in the results of the economic outcomes arising from the different instruments used to derive utilities may be explained by the limited recall periods used in these measures and their focus only on health-related QoL. These conflicting findings suggest that these measures may be capturing different aspects of QoL, which clearly has an impact on the results. Further consideration of alternative measures to assess cost-effectiveness, such as willingness to pay, which provides a broader assessment of well-being, is also needed.

Trial registration

This trial is registered as ISRCTN86566246.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 02/06/02. The contractual start date was in November 2004. The draft report began editorial review in February 2015 and was accepted for publication in May 2015. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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