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Usual medical treatments or levonorgestrel intrauterine system for women with heavy menstrual bleeding in primary care: Long-term pragmatic trial

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ABSTRACT

Background: Heavy menstrual bleeding (HMB) is a common, chronic problem burdening women and health services. However long-term evidence on treatment in primary care is lacking.

Aim: To assess the effectiveness of commencing levonorgestrel intra-uterine system (LNG-IUS) or usual medical treatments for women presenting with HMB in general practice.

Design: Pragmatic, multicentre, parallel, open-label randomised controlled trial

Setting: 63 primary care practices

Methods: 571 women, aged 25-50, with HMB were randomised to LNG-IUS or usual medical treatment (tranexamic/mefenamic acid, combined oestrogen-progestogen, or progesterone alone). The primary outcome was the patient reported Menorrhagia Multi-Attribute Scale (MMAS, measuring effect of HMB on practical difficulties, social life, psychological and physical health, work and family life; scores from 0 -100). Secondary outcomes included surgical intervention (endometrial ablation/hysterectomy), general quality-of-life, sexual-activity and safety.

Results: At five years post-randomisation 424 (74%) women provided data. While the difference between LNG-IUS and usual-treatment groups was not significant (3.9 points; 95% CI: -0.6 to 8.3; $p=0.09$), MMAS scores improved significantly in both groups from baseline (mean increase, 44.9 and 43.4 points, respectively; $p<0.001$ for both comparisons). Rates of surgical intervention were low in both groups (surgery-free survival was 80% and 77%; HR: 0.90; 95%CI: 0.62 to 1.31; $p=0.6$). There was no difference in generic quality of life, sexual-activity scores or serious adverse events.

Conclusion: Large improvements in symptom relief across both groups show treatment for heavy menstrual bleeding can be successfully initiated in primary care with long-term benefit for women, and with only modest need for surgery.

Trial Registration: International Clinical Trial Registry Number: 86566246

Introduction

Heavy menstrual bleeding (HMB) is a common and debilitating problem that can significantly affect women's lives. With an annual community incidence of 25% among women aged 18-54,¹ one million women seek help for this problem each year in the UK², mostly in general practice,³ and it accounts for 12% of all gynaecology referrals.⁴ Despite the many factors influencing women's decisions not to seek help,⁵ the cost of health care for HMB is substantial. In a recent national audit of care of HMB in England and Wales, almost a third of women had received no previous medical treatment before referral to secondary care, with over 40% of women having surgical intervention in the year following first attendance at hospital.⁶

The National Institute of Clinical and Healthcare Excellence (NICE) defines heavy menstrual bleeding as that which interferes with a woman's physical, emotional, social and material quality of life, and which can occur alone or with other symptoms.² This recognises women's perceptions of heavy menstrual bleeding and what they find troublesome does not correlate well with a traditional biomedical focus on volume of blood loss.⁷ For clinical practice, HMB should be regarded as more subjectively defined by women, focusing on perceived impact on their lives rather than menstrual blood loss in itself^{2,8}; in addition to physical and psychological health, this includes interference with social, working and family life or practical burden of sanitary care.⁹

At the commencement of the current trial, guidelines for HMB recommended initial management should usually be medical, using either oral tranexamic acid or mefenamic acid; or using the combined oral contraceptive (COC), or the levonorgestrel-releasing intrauterine system (LNG-IUS) for women requiring contraception, or for those not requiring contraception but prepared to accept hormonal treatments.¹⁰ In 2007, similar guidelines from NICE recommended this range of pharmaceutical treatments, and underlined the potential for more women with HMB to be managed by their general practitioners (GPs), avoiding secondary care.²

Five trials in gynaecological settings (involving 44-165 women, and 3-12 months follow up) have found LNG-IUS more beneficial in reducing menstrual blood loss than treatments such as mefenamic acid or COC.¹¹ However evidence on how helpful treatments are in improving women's quality of life, or their use in primary care, is lacking.¹¹ Our earlier findings from the current trial found both LNG-IUS and usual medical treatments significantly reduced the effect of HMB on women's quality of life in the first two years of treatment, but LNG-IUS was the more effective.¹² However HMB may be chronic and episodic over several years.¹³ A recent Cochrane review recommended trials of at least five years are needed, which should include a focus on women's quality of life.¹¹

Women's and their GPs' decisions about medical treatments for HMB also include wider dynamic considerations such as women's attitudes to using oral treatment or having an intrauterine device, changing plans about wanting to conceive or need for contraception, or anticipating surgical intervention. Thus, long-term evidence is needed to help guide decision-making in practice.

In this pragmatic randomised controlled trial, we assessed outcomes at five years of commencing LNG-IUS or usual medical treatments for women presenting with HMB in primary care.

Methods

Population

Women between 25 and 50 years of age who presented to their GP, affected with HMB involving at least three consecutive menstrual 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, had intermenstrual bleeding (between expected periods), postcoital bleeding or findings suggestive of fibroids (abdominally palpable uterus equivalent in size to that at 10 to 12 weeks' gestation) or other disorders, or had contraindications to or a preference for either the levonorgestrel- IUS or usual medical treatments. Women with heavy, irregular bleeding were ineligible unless the results of endometrial biopsy were reported to be normal; no further investigations were mandated by the protocol. All patients provided written informed consent.

Randomization

Patients were assigned to a study group by telephone or a Web-based central randomization service at the University of Birmingham Clinical Trials Unit. A computerized, minimized randomization procedure was used to achieve balance between the groups with respect to age (<35 years or ≥35 years), body-mass index (BMI; the weight in kilograms divided by the square of the height in metres) (≤25 or >25), duration of symptoms (<1 year or ≥1 year), need for contraception (yes or no), and HMB alone or HMB accompanied by menstrual pain.

Study interventions and compliance

Eligible women who provided written informed consent were randomly assigned to either LNG-IUS or usual medical treatment. Usual treatment options included oral tranexamic acid, mefenamic acid, norethisterone, a combined oestrogen–progestogen or progesterone-only oral contraceptive pill (any formulation); or medroxyprogesterone acetate injection and were chosen by the clinician and patient on the basis of any contraceptive needs or the desire to avoid hormonal treatment.^{2,14} The particular medical treatment to be used was specified before randomization. Subsequently, and in line with real life practice, treatments could be changed (from one medical treatment to another,

from the LNG-IUS to a usual medical treatment, or from a usual medical treatment to the LNG-IUS), or could be discontinued because of a perceived lack of benefit, side effects, a change in the need for contraception, referral for endometrial ablation or hysterectomy, or any other reasons according to usual clinical practice.^{2,14} Treatment changes reported by women were confirmed with their GP.

Outcome measures and follow-up

The primary outcome measure was the patient reported, condition-specific Menorrhagia Multi-Attribute Scale (MMAS) at five years follow-up.^{15,16} The MMAS is designed to measure the effect of heavy menstrual bleeding on six domains of daily life. Possible responses are: not affected/slightly affected/moderately affected/severely affected for each domain. The scores for each domain are weighted according to the perceived importance of that domain to women with this condition. In order of importance, from highest to lowest, the domains are: family life and relationships; physical health; work and daily routine; practical difficulties; psychological health; social life. Summary scores, which range from zero (severely affected) to 100 (not affected), were assessed. The MMAS has a high degree of reliability and internal consistency,¹⁵ has good content and construct validity,^{17,18} is responsive^{19,20} and is acceptable to respondents.^{15,16,19,20}

Secondary outcome measures included general health-related quality of life and sexual activity. To assess generic quality of life, we used three instruments: the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), version 2 (with scores ranging from zero [severely affected] to 100 [not affected]); the EuroQoL Group 5-Dimension Self- Report Questionnaire (EQ-5D) descriptive system (with scores ranging from -0.59 [health state worse than death] to 100 [perfect health state]); and the EQ-5D visual-analogue scale (with scores ranging from zero [worst health state imaginable] to 100 [most perfect health state imaginable]). The validated Sexual Activity Questionnaire measures pleasure (with scores ranging from zero [lowest level] to 18 [highest level]), discomfort (with scores ranging from zero [greatest] to 6 [none]), and frequency (assessed relative to perceived usual activity as an ordinal response).²¹ Responses for all outcomes were obtained before randomization and by mail at five years after randomization. Data were collected from participating GPs regarding all

serious adverse events, defined as adverse events that resulted in death, disability, or hospitalization. Patients were also asked to report any hospitalizations and adverse events leading to discontinuation of the study treatments.

Study oversight

Study oversight was provided by an independent steering committee and an independent data and safety monitoring committee, whose three reviews of interim data provided no reason to modify the trial protocol on the basis of pragmatic stopping criteria.²² The study was conducted in accordance with the protocol, available at <http://www.nets.nihr.ac.uk/projects/hta/020602>. Approval of the study was obtained from the South-West England Multicentre Research Ethics Committee, and clinical trial authorization was received from the Medicines and Healthcare Products Regulatory Authority. All medications and devices were prescribed by providers through the National Health Service. The manufacturers of any therapeutic agents used in the study were not involved in any aspect of the trial.

Statistical considerations

The study was designed to have 90% power (at $p < 0.05$) to detect a small-to-moderate difference²³ - 0.3 of a standard deviation - in the primary outcome. This required responses from 470 patients; we increased the sample size to 570 to allow for up to 20% loss to follow-up. At five years follow up we received 424 responses; a post-hoc calculation suggested this total would provide 87% power ($p = 0.05$) to detect the same size of difference. For progression to surgical intervention (hysterectomy or endometrial ablation), using an assumed rate of 35% in the standard arm (a figure that was set out in the protocol), 424 women would provide 80% power ($p = 0.05$) to detect an absolute reduction of 12%, i.e. 35% down to 23%.

Analyses were performed according to the intention-to-treat principle. Differences between groups at five years were examined by analysis of covariance (adjusting for baseline score). Changes between baseline score within groups were examined using paired t-tests. The primary analysis was

based on the fact that some patients declined to complete the MMAS, indicating on the form that they were no longer bleeding and the questions did not appear relevant to them. Thus, these patients were assigned the best possible score (100). This assumption was further tested through sensitivity analyses by making no assumption about those questionnaires that were returned blank, i.e. MMAS scores were assumed to be missing.

Kaplan-Meier plots were constructed for a time to surgery and a time to treatment change analysis, with women censored at date to last follow-up or, if appropriate, date to death, withdrawal or loss to follow-up. A Cox proportional hazards model was used to construct hazard ratios. Surgery-free analysis was then re-performed, excluding participants who crossed over from one treatment group to another. All the effect sizes are presented with 95% confidence intervals and p-values. All tests and corresponding p-values were two-sided. The statistical package SAS 9.2 was used for all the statistical analysis.

Results

Patients and follow-up

Between February 2005 and July 2009, a total of 571 women with heavy menstrual bleeding from 63 primary care centres were randomly assigned to either the LNG-IUS (285 women) or usual medical treatment (286 women). Baseline characteristics were similar between the two treatment groups (Table 1). For 215 (75%) of the women assigned to usual medical treatment, the initial prescription was for mefenamic acid, tranexamic acid, or a combination of the two drugs; 55 (19%) of the women in the usual-treatment group required contraception.

Study-questionnaire booklets were returned by 424 (74%) of participants at five years (Fig. 1). One hundred and fifteen women (27%) indicated they were no longer having periods and so did not complete the MMAS section. These women completed other sections of the questionnaire and still contributed to the analysis of MMAS responses (see statistical considerations).

The proportion of patients still taking their allocated treatment at five years was 47% (95%CI: 40% to 52%) in the LNG-IUS group and 15% (95%CI: 11% to 20%) in the usual-treatment group (Fig. 2). Of the 228 recorded instances of treatment change in women allocated usual medical treatment, 97 (43%) were to LNG-IUS. In the LNG-IUS group, 57/148 (39%) treatment switches were to usual-treatment. Reported reasons for discontinuation of treatment were varied, with lack of treatment efficacy most commonly cited (24% [36/148] in the LNG-IUS group and 41% [94/228] in the usual-treatment group. Further details are summarised in Tables 1.1 and 1.2 of the appendix.

Primary outcome - MMAS

Women started out with average scores approximately 40 points out of 100 on the MMAS, indicating they were substantially affected by HMB at presentation to their GP. At five years, these scores were significantly improved to over 80 points out of 100 in both groups (Table 2). This improvement was higher on average among women assigned to LNG-IUS but the difference was not statistically significant (3.9 points; 95% confidence interval [CI], -0.6 to 8.3; $p=0.09$). The same analysis without any assumption about MMAS scores, where the form was returned blank and the woman indicated she was no longer bleeding, returned a similar result (5.2 points difference in favour of LNG-IUS; 95% confidence interval [CI], -0.4 to 10.8; $p=0.07$).

Surgical interventions

Fifty-three events (endometrial ablation or hysterectomy) in the LNG-IUS group versus 56 in the usual-treatment group were included in the surgery-free survival analysis (109 events in total). This difference was not statistically significant (HR: 0.90; 95%CI: 0.62 to 1.31; $p=0.6$) (Fig. 3). Analysis excluding participants who crossed over from one group to another returned a similar result (HR: 0.96; 95%CI: 0.60 to 1.52; $p=0.9$). Five-year surgery-free survival rates were 80% (95%CI: 74% to 84%) in the LNG-IUS group versus 77% (95%CI: 71% to 82%) in the usual-treatment group. In total, there were 115 surgical interventions: 24 ablations in the LNG-IUS group versus 31 in the usual-treatment

group and 30 hysterectomies in both groups (six more events than quoted above as six patients had both types of surgery).

Generic quality of life and sexual activity

Responses to the Euroqol and SF-36 instruments were generally significantly improved from baseline in both groups (Table 3); the only statistically significant difference between groups was seen in the general health perception domain of the SF-36 and favoured LNG-IUS (4.7 points, 95%CI: 0.6 points to 8.8 points; $p=0.02$). The treatment groups did not differ significantly with respect to any of the domains of the Sexual Activity Questionnaire.

Safety

There was no significant difference between the groups in the total number of serious adverse events ($p=0.32$). These are listed in Table 2 of the appendix.

Discussion

This pragmatic trial shows women affected by heavy menstrual bleeding can be effectively helped in primary care by initiating LNG-IUS or usual medical treatment, with long-term benefit, and only modest need for surgery. Women in either treatment group experienced similar and significant improvement in condition-specific quality of life after five years. Women receiving usual medical treatment were no more likely to need surgical intervention than those treated with insertion of an LNG-IUS, with rates of surgical intervention (endometrial ablation, hysterectomy) remaining low in both groups (approximately 20%). Generic quality of life scores were similarly improved in both groups and there was no difference in sexual-activity scores or serious adverse events.

Strengths and weaknesses

This is the largest randomised trial available of medical treatments for HMB. Generalisability is strengthened by a pragmatic, multicentre design, mimicking treatment decisions in 'real life' primary

care, involving a large sample ethnically representative of the UK population. Outcomes have been assessed in the longer term, appropriate to the chronic nature of HMB. We used a validated patient-centred primary outcome reflecting women's assessments of the impact of HMB on their quality of life, in line with guidance for assessing HMB,² rather than a biomedical focus on menstrual blood loss itself. While use of indirect measures of menstrual blood loss were considered, pictorial blood assessment charts correlate poorly with blood loss and are not consistently accurate.⁸

Given five years since study entry, a relatively high follow up has been sustained to include 424 of 571 (74%) women randomised. The range of drugs within the usual medical treatment group includes those used in routine practice, but we acknowledge this limits ability to compare any individually with the LNG-IUS. The intention-to-treat analysis may be considered overly conservative by some – particularly given the long follow-up period - but alternatives such as per protocol analyses are likely to exaggerate treatment effects as they restrict analyses to only those patients happy with treatment performance.²⁴ While there was no statistically significant difference in primary outcome between the two groups, we note significant proportions of women reported their periods had ceased, or had changed or ceased treatments, and this may have limited the ability to detect a difference. However such changes might be expected in real life over five years and are consistent with experience from national audit of care for HMB.⁶

Relation to other studies

A 2015 Cochrane review highlights lack of research on medical management of HMB in primary care, the need for evidence on HMB related quality of life outcomes, and for data from longer term trials reporting beyond two years.¹¹ The current trial contributes new evidence to these three gaps. We are not aware of similar long term comparisons of medical treatments initiated in primary care. In secondary care, trials of similar length have compared LNG-IUS to hysterectomy²⁵ rather than other medical treatments, or endometrial resection to oral medication.²⁶

Our results are encouraging in showing both HMB-specific and generic quality of life for women were significantly improved five years after commencing either usual medical treatment or LNG-IUS. The size of improvement – approximately equivalent to two standard deviations - is likely to be a very large effect.²³ Women were considerably affected by HMB at presentation to their GP, and improvement in MMAS score from baseline (by 43.9 and 44.9 points for usual medical treatment or for LNG-IUS respectively) reflects a clinical change of at least one category in all six MMAS domains: (practical difficulties, social life, psychological health, physical health, work and daily routine, and family life and relationships), from being substantially to minimally affected by HMB, for example, from frequent to occasional disruptions of work and daily routine.

The greater clinical efficacy of LNG-IUS compared to usual medical treatments seen at two years in this trial¹² has now diminished. At five years, only a borderline difference ($p=0.09$) in favour of LNG-IUS has been observed. This was estimated to be 3.9 points on average which is less than one-fifth of a standard deviation and unlikely to be clinically meaningful. We note this may be unsurprising given the high proportions of women who, by five years after treatment allocation, had either changed to a treatment that worked for them, or had ceased bleeding either naturally or through surgical intervention. Retention rates at five years were 15% with usual medical treatment and 47% in the LNG-IUS group. This may reflect greater impact on symptoms of LNG-IUS. Another factor may be that women could more easily choose to stop usual medical treatment when desired or according to their symptoms, without need for consultation and removal of their intra-uterine device.

Similar reasons may explain our data providing no evidence of any reduction in surgical interventions with LNG-IUS compared to usual medical therapy, even when we discounted treatment cross-overs. At two years post-randomisation, surgical interventions were low at about 10% in both medical treatment groups¹² and this has approximately doubled to 20% in both groups at five years. This is still much lower than the 58% surgical intervention rate at two years identified in an earlier Cochrane

review of trials comparing oral medical therapy to surgical interventions for HMB, though these were in secondary care settings.²⁷ The relatively low surgical intervention rates in the current trial may also possibly be explained by the exclusion of women with enlarged uteri or known disease such as fibroids that were deemed unsuitable for treatment in a community setting.

Implications for clinical practice

Our data have been obtained in the context of real life clinical practice, for a chronic and episodic problem, where, as experienced in this trial, women may commonly discontinue or change treatments for their HMB.⁶ The inclusion criteria also underline that women who do not have a uterus palpable abdominally, or who have had normal investigation for irregular periods, can be successfully treated in primary care.

The results provide valuable practical information for women and GPs when weighing up choice of, and what to expect in the longer term from treatments for HMB. This needs to take account of individual women's differing preferences for oral treatments or insertion of an intra-uterine device left *in situ* and changing needs for contraception or fertility.²⁸ The study shows women can benefit significantly from choosing either usual medical or LNG-IUS treatment. Just under half of women might be expected to retain their LNG-IUS at five years, while most women have ceased usual oral treatments by this stage. Women able to choose LNG-IUS, if suited to their circumstances, may experience less discontinuation of treatment, and a better effect at two years¹². However it will not suit all women - 36% in the current trial had had their LNG-IUS removed by two years because of persisting HMB or unpredictability of bleeding¹² and this is a well-recognised problem²⁹.

The low rates of progression to surgical intervention observed, five years from initial presentation with HMB to their GP, emphasise the feasibility and importance of treating women with HMB in primary care. Avoiding referrals to secondary care may reduce high operative intervention rates.^{6, 30}

Wider public awareness is needed to encourage women to seek help for HMB as they are likely to benefit from LNG-IUS or usual medical treatment in primary care. Commensurate availability of expertise to offer this range of medical treatments should be ensured. While our data suggest the earlier superiority of LNG-IUS over the first two years was not sustained at five years, further research to confirm this by assessing women's satisfaction with and the acceptability of treatments would be helpful. Longitudinal qualitative research is needed to explore and understand women's decisions in choosing treatments for HMB and experiences of using them over the time. We intend to follow up patients to ten years when we expect that around half of our cohort will have reached the menopause to assess further patterns of treatment use, and surgical intervention rates.

This pragmatic trial confirms women affected by HMB, with no significant clinical risk factors on history or examination, can be safely helped by initiating medical treatments in primary care, with long term benefit in reducing the effects of HMB on their quality of life.

How this fits in

Heavy menstrual bleeding is a chronic debilitating problem, and common cause of gynaecological referral and surgery. We lack evidence about long-term effectiveness of treatment in primary care. This trial shows women affected by this problem, with no significant clinical risk factors on history or examination, can be safely helped by starting either usual medical treatments or levonorgestrel intrauterine system in general practice. These treatments reduce the effects of heavy menstrual bleeding on women's lives over a five-year time course, with most avoiding surgical intervention.

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Contributors statement

JK, JG, JD and HP designed the study as grant co-applicants. JK and JG were the co-principal investigators and supervised the trial, with other authors contributing to ongoing management of the trial. The ECLIPSE collaborative group recruited patients to the trial. KT and LM performed the statistical analysis. The paper was written by JK and LM. All authors contributed to

the interpretation of results and approved the paper. The Birmingham Clinical Trials Unit did the randomisation, data management and central monitoring.

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Neither the funder nor sponsor had any role in study design, data collection, interpretation or analysis, or in writing the report for publication. The authors had full access to all the data from the study. The authors vouch for the accuracy and completeness of the data and analyses.

Ethical approval

Approval of the study was obtained from the South-West England Multicentre Research Ethics Committee on 18th August 2004, and clinical trial authorisation was received from the Medicines and Healthcare Products Regulatory Authority on 16th September 2004.

Conflict of Interest statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). All authors report no conflicts of interest.

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