Medical treatment for heavy menstrual bleeding in primary care: 10-year data from the ECLIPSE trial

Abstract

Background
Heavy menstrual bleeding (HMB) is a common problem that can significantly affect women's lives. There is a lack of evidence on long-term outcomes after seeking treatment.

Aim
To assess continuation rates of medical treatments and rates of surgery in women 10 years after initial management for HMB in primary care.

Design and setting
This was a prospective observational cohort study.

Method
Women with HMB who participated in the ECLIPSE primary care trial (ISRCTN86566246) completed questionnaires 10 years after randomisation to the levonorgestrel-releasing intrauterine system (LNG-IUS) or other usual medical treatments (oral tranexamic acid, mefenamic acid, combined oestrogen–progestogen; or progestrone alone).

Results
The responding cohort of 266 women was demographically and clinically representative of the original trial population. Mean age at baseline was 41.9 years (SD 4.9) and 53.7 years (SD 5.1) at follow-up. Over the 10-year follow-up, 60 of 206 (29.1%) women had surgery (hysterectomy n=34, 16.5%; endometrial ablation n = 26, 12.6%). Between 5 and 10 years, 89 women (43.2%) ceased all medical treatments and 88 (42.7%) used LNG-IUS alone or in combination with other treatments.

Conclusion
Medical treatments for women with HMB can be successfully initiated in primary care, with low rates of surgery and improvement in quality of life observed a decade later.

Keywords
cohort studies, endometrial ablation techniques; female; hysterectomy; menorrhagia; primary health care; quality of life.

INTRODUCTION
Heavy menstrual bleeding (HMB) is a common problem that can significantly affect women's lives until menopause. Although diagnostic definitions using menstrual blood loss exist, it is the impact on a woman's physical, emotional, social, and economic quality of life that guides treatment.¹ ²

In 2007, the National Institute for Health and Care Excellence (NICE) published guidelines for HMB, updating them in 2018. These recommend starting medical treatment for HMB without investigation if history and/or examination suggest low risk of uterine pathology; or taking account of history and examination, following ultrasound and/or hysteroscopy to exclude this. The levonorgestrel-releasing intrauterine system (LNG-IUS) is recommended as first-line treatment for women with no uterine pathology, or the use of other medical treatments if LNG-IUS is declined or not suitable (tranexamic acid, non-steroidal anti-inflammatory drugs, combined hormonal contraception, oral progestogens).³ NICE emphasises clinical consideration be given to comorbidities, presence of fibroids, adenomyosis or endometrial polyps, contraceptive need, and women's preferences for first-line treatment. If medical treatments fail to provide effective relief, surgical procedures should be considered.¹

The NICE recommendations were supported by findings from the original ECLIPSE trial, which randomised 571 women, aged 25 to 50 years, presenting to primary care with HMB to either the LNG-IUS or other usual medical treatment (oral tranexamic acid, mefenamic acid, combined oral contraceptive pill, or progesterone alone, chosen as clinically appropriate by the GP and woman) (ISRCTN86566246).³ Women’s eligibility for the original trial, and their clinical assessment consistent with current NICE guidance, are detailed in the Supplementary Information S1. The primary outcome was a patient-reported score of the burden of HMB,⁴ assessed over a 2-year period. This improved significantly from baseline in both groups across all timepoints, although the improvements in women in the LNG-IUS group were significantly greater than those assigned usual medical treatment at 2-year follow-up.³ By 5-year follow-up, the benefit of LNG-IUS was reduced.⁵ Consequently, NICE also indicated that the usual medical treatments offered in ECLIPSE be considered for women unable or unwilling to use the LNG-IUS.

To the authors’ knowledge, there is no available research on medical treatment of HMB in the longer term in primary care.

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beyond the 5-year data from the ECLIPSE trial. Although women’s need for treatment may be expected to change approaching menopause, further evidence is needed to help inform patient and clinical decision making. The primary objective of this study was to assess continuation rates of medical treatments, and rates of surgical interventions, in women 10 years after initial management for HMB in primary care.

**METHOD**

The ECLIPSE trial ended from a regulatory perspective at 5-year follow-up. However, data collection continued for this prospective observational study to 10 years. The original trial randomised women between 25 and 50 years of age who presented to their GP with HMB involving at least three consecutive menstrual cycles. The randomisation and interventions used have been previously reported. Women could subsequently swap or cease their allocated treatment. The aim of the current study was to collect 10-year data from 276 women, equating to 48.3% of the 571 women originally randomised (Figure 1). This target anticipated further loss to follow-up because of the length of time elapsed since previous contact at 2 or 5 years, relocation, non-completion of questionnaire, or death. The process of recontacting and reconsenting participants is described in Supplementary Information S1.

All data were collected directly by questionnaire (paper or via link to online form). The primary outcomes were use of treatments for HMB, and the surgical interventions of hysterectomy and endometrial ablation. Generic quality of life was assessed using the Short-Form Health Survey (SF-36, version 2, with scores ranging from 0 [severely affected] to 100 [not affected]); the EuroQoL 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 0 [worst health state imaginable] to 100 [most perfect health state imaginable]). The Sexual Activity Questionnaire (SAQ) measured pleasure (with scores ranging from 0 [lowest level] to 18 [highest level]), discomfort (with scores ranging from 0 [greatest] to 6 [none]), and frequency. The patient-reported, condition-specific Menorrhagia Multi-Attribute Scale (MMAS) at 2-year follow-up was the primary outcome for the ECLIPSE trial. As the MMAS only seeks responses in relation to current HMB, completion was optional as it was anticipated to not be relevant to the majority of women at 10-year follow-up. Originally, manual extraction of data

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**How this fits in**

Heavy menstrual bleeding (HMB) is a common problem and reason to seek treatment in primary care. It is not known how women then fare in the long term, in order to inform patient and clinical decision making. To the authors’ knowledge, this research is the first to report what proportions of women may be expected to continue to use LNG-IUS (Mirena) or other medical treatments (oral tranexamic acid, mefenamic acid, combined oestrogen-progestogen, or progesterone alone), or progress to surgical intervention, a decade after GP treatment for HMB. It shows that medical treatments for women with HMB can be initiated in primary care with low subsequent rates of surgery and improvement in quality of life 10 years later.

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**Figure 1. Progression of participants from the original ECLIPSE trial to the observational study. Attempts to contact women after 23 March 2020 were curtailed because of the COVID-19 pandemic (Supplementary Information S1).**
The progression of women available to be contacted from the original trial to women in the current study (hereafter called responders) are shown in Figure 1. A total of 206 women provided reconsent and returned completed 10-year follow-up data by 31 March 2020 (200 by mail, six online).

The baseline (before randomisation) characteristics of responders and those who were not followed-up are presented in Table 1. Responders were very similar to those women not followed up, with an average age of 41.9 and 41.1 years, respectively, and did not differ clinically in their initial symptoms and presentations of HMB.
Of the 206 women, 40 were not in an intimate relationship and 116 reported via the SAQ that they were sexually active. There were improvements over time in SF-36 scores in all domains, except general health perception and physical functioning, and in EQ-5D scores. These improvements occurred in both groups, with small and statistically insignificant differences between the randomised groups in any domain of the three questionnaires. Only 13 responders, 12 of whom described their bleeding as heavy, completed the MMAS questionnaire, indicating at least 56.3% of women were sexually active.

Table 4 presents scores for these three questionnaires by randomised group at baseline and at 10-year follow-up, including only those women who completed questionnaires at both timepoints. There were improvements over time in SF-36 scores in all domains, except general health perception and physical functioning, and in EQ-5D scores. These improvements occurred in both groups, with small and statistically insignificant differences between groups.

Of the 206 women, 40 were not in an intimate relationship and 116 reported via the SAQ that they were sexually active. There was a clear deterioration within the discomfort domain of the SAQ, although with no evidence of a difference between groups.
the allocation groups, but no changes were seen within the pleasure domain.

**Surgical interventions**

Over the 10-year follow-up period, there were 60 of 206 (29.1%) women who had had surgical intervention, including hysterectomy (n = 34, 16.5%) or endometrial ablation (n = 26, 12.6%). No woman had both procedures and no one who had a surgical procedure reported HMB at 10 years. The cumulative rate of surgery was slightly lower in women initially allocated to LNG-IUS (28/110 women, 25.5%) compared with those allocated to standard medical treatment (32/96, 33.3%), (data not shown) in the ECLIPSE trial. Considering the opposite outcome, the surgery-free rate, including all data collected over a median of 11.2 years, the cumulative surgery-free rate was 74% for LNG-IUS and 65% for usual medical treatment, shown in Figure 2, and the difference was not statistically significant (hazard ratio 0.73, 95% confidence = 0.44 to 1.21, \( P=0.22 \)).

**DISCUSSION**

**Summary**

This study shows medical treatments for women with HMB can be initiated in primary care with improvement in quality of life and high likelihood of avoiding surgery 10 years later. Among women, typically presenting with HMB in their early forties, this study found that half reach the menopause in the ensuing decade and over 40% may be expected to cease medical treatments over this time. However, a similar proportion (42.7%) continue to use LNG-IUS alone or in combination with other oral treatments, and almost 30% were using LNG-IUS after 10 years.

Relatively low rates of surgical intervention were sustained at 29% after 10 years, modestly increased from those at 5 (around 20%) and 2 (around 10%) years after commencing treatment in primary care. Women initially treated with LNG-IUS were slightly less likely to need surgical intervention than those commenced on standard medical treatments, however, this was not statistically or clinically significant. There were improvements over time in generic quality-of-life scores in both women who were initially allocated LNG-IUS or to other usual medical treatment, but with no evidence of any significant differences between the two original groups.

**Strengths and limitations**

This research has ascertained outcomes in women a decade after initial treatment for HMB in primary care, following participation in the largest trial of medical treatments for HMB. Responses were achieved from 206 women, 206/571, 36.1% of the original trial population and 206/490, 42.0% of those potentially available for recontact after 10 years. Although this was lower than anticipated because of difficulties during
<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Baseline scores</th>
<th>Change within group</th>
<th>Difference between groups over 10 years, mean (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SF-36</strong></td>
<td></td>
<td></td>
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<tr>
<td>Physical functioning</td>
<td>84.0 (81.5 to 86.5)</td>
<td>-0.9 (-4.4 to 2.6)</td>
<td>2.8 (-5.7 to 0.9)</td>
<td>0.786</td>
</tr>
<tr>
<td>Physical role</td>
<td>74.0 (71.0 to 76.9)</td>
<td>-1.3 (-5.4 to 2.8)</td>
<td>6.0 (2.7 to 9.3)</td>
<td>0.038</td>
</tr>
<tr>
<td>Emotional role</td>
<td>72.4 (69.4 to 75.5)</td>
<td>-0.8 (-4.9 to 3.2)</td>
<td>7.4 (4.2 to 10.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>Social functioning</td>
<td>67.2 (64.4 to 70.0)</td>
<td>-1.7 (-5.6 to 2.2)</td>
<td>7.9 (4.8 to 10.9)</td>
<td>0.007</td>
</tr>
<tr>
<td>Mental health</td>
<td>61.7 (59.0 to 64.4)</td>
<td>-0.8 (-4.9 to 3.2)</td>
<td>6.3 (3.7 to 9.0)</td>
<td>&lt;0.001</td>
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<tr>
<td>Energy and vitality</td>
<td>41.6 (38.8 to 44.4)</td>
<td>-1.7 (-5.6 to 2.2)</td>
<td>6.7 (3.8 to 9.6)</td>
<td>&lt;0.001</td>
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<tr>
<td>Pain</td>
<td>49.0 (46.1 to 51.9)</td>
<td>-2.3 (-6.4 to 1.8)</td>
<td>9.5 (6.5 to 12.6)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>EuroQol EQ-5D</strong></td>
<td></td>
<td></td>
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<tr>
<td>Descriptive system</td>
<td>0.78 (0.50 to 1.07)</td>
<td>-0.1 (-0.39 to 0.37)</td>
<td>-0.03 (-0.33 to 0.28)</td>
<td>0.270</td>
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<tr>
<td>Visual analogue scale</td>
<td>70.3 (67.3 to 73.3)</td>
<td>-1.1 (-3.2 to 0.0)</td>
<td>-1.5 (-3.5 to -0.5)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Scores are only calculated for women providing both baseline and 10-year data. SF-36 = 36-item Short-Form Health Survey. EuroQol EQ-5D = EuroQol-5 Dimensional System.*

The original trial and current study follow-up population reflect the ethnic diversity of England and Wales when women were recruited (87% White, 13% Black/Asian/Other in 2011 UK census). However, it is recognised that further research with women from Black and ethnic minority communities is needed as HMB experiences may differ, especially given the higher prevalence of fibroids in Black women.

Given the proportion of participants who had changed or ceased their original allocated treatments by 5 years, it was anticipated that intention-to-treat comparisons at 10 years would have limited ability to demonstrate a difference for the participant-reported quality-of-life instruments. A large proportion of women had, as expected, stopped having periods, either because of the menopause, or surgical treatment, meaning few women were able to report on the original primary outcome measure, the MMAS. Nevertheless, it has been possible to illustrate for the first time the proportion of women progressing to surgical intervention by initial medical treatment.

The original intention had been to collect data from GP records, but cross-checking against women’s self-reported data suggested this did not add value. As GP practices then became inaccessible to researchers during the COVID-19 pandemic, the potential for missing data exists but is probably limited. Women’s own knowledge and reporting of whether they had an LNG-IUS in situ or not, their use of other oral medical treatments, their perception of being perimenopausal or of having surgery, is likely to be accurate and using this in the current study was the most realistically achievable option. Participating women’s qualitative experiences of HMB and influences on their treatment over time will be reported separately in a future article.

Comparison with existing literature
To the authors’ knowledge, this study is the first to report outcomes a decade after commencing medical treatment for HMB in primary care. Evidence from the height of the COVID-19 pandemic, such long-term data for women with HMB, to the authors’ knowledge, have not been available before, nor at this scale. Responding women were very similar, both demographically and clinically at presentation, to non-responders, lending confidence in the generalisability of the trajectories reported.
The sustained low rates of progression to surgical intervention observed, and general improvement in quality of life, 10 years from women’s initial presentation, underline the importance and value of initiating medical management of women’s HMB in primary care, where most women seek help from health services. Avoiding referrals to secondary care is likely to reduce operative intervention rates. The findings provide helpful information for women and GPs on what to expect in the longer term from starting treatments for HMB and to inform individual decision making. This includes women’s chances of surgery, of continuing or ceasing medical treatments, and an accurate estimate of 10-year retention of LNG-IUS.

Wider public awareness is also needed to encourage women to seek help for HMB if it is affecting their lives, as they are likely to benefit from treatments commenced in the community setting. Ongoing care should ensure clinical willingness to continue review of women’s response, their working diagnosis, need for further investigation or different treatment, or surgical options over time. This should include counselling in those women considering removal or renewal of LNG-IUS at 5 years so that they may continue to benefit and avoid surgery.

In conclusion, the study provides a helpful new indication of expected proportions of women continuing to use or not use treatments for HMB, or progressing to surgical intervention, and of the significant proportion of women using LNG-IUS after a decade. Medical treatments for women with HMB can be initiated in primary care with low rates of surgical intervention and improvement in quality of life observed 10 years later. The study supports current NICE recommendations\(^1\) on medical management of HMB, and confirms many women with HMB do not require surgery as there are less invasive and acceptable alternatives.
REFERENCES


