Accepted Manuscript

British Journal of General Practice

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

Kai, Joe; Dutton, Brittany; Vinogradova, Yana; Hilken, Nicholas; Gupta, Janesh; Daniels, Jane

DOI: https://doi.org/10.3399/BJGP.2022.0260

To access the most recent version of this article, please click the DOI URL in the line above.

Received 23 May 2022
Revised 05 September 2022
Accepted 09 September 2022

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

Joe Kai, GP & Professor of Primary Care [1]
Brittany Dutton, Research Associate [1]
Yana Vinogradova, Senior Research Fellow [1]
Nicholas Hilken, Senior Database Developer [2]
Janesh Gupta, Professor of Obstetrics & Gynaecology[3]
Jane Daniels, Professor of Clinical Trials [2]

[1]Centre for Academic Primary Care, University of Nottingham, England
[2]Nottingham Clinical Trials Unit, University of Nottingham, England
[3]Centre for Women's and Newborn Health, University of Birmingham, England

Corresponding:

Joe Kai, GP & Professor of Primary Care
Centre for Academic Primary Care
Applied Health Research Building
University Park, Nottingham, United Kingdom, NG7 2RD
Joe.kai@nottingham.ac.uk
https://orcid.org/0000-0001-9040-9384

Word count = 2771
(4 tables, 2 figures, 1 supplementary appendix)

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

Prospective observational cohort study.

Methods

Women with HMB who participated in the ECLIPSE primary care trial (ISRCTN86566246) completed questionnaires 10 years after randomisation to levonorgestrel-releasing intra-uterine system (LNG-IUS) or other usual medical treatments (oral tranexamic acid, mefenamic acid, combined oestrogen–progestogen; or progesterone alone). Outcomes were rates of surgery, medical treatments and quality of life using SF-36 and EQ-5D.

Results

The responding cohort of 206 women was demographically and clinically representative of the original trial population. Mean age at *baseline was 41.9 (SD 4.9)* and 53.7 years (SD 5.1) at follow up. Over the 10-year follow-up, 60 of 206 (29%) women had surgery (hysterectomy 34 [17%], endometrial ablation 26 [13%]). Between 5 and 10 years, 89 women (43%) ceased all medical treatments and 88 (43%) used LNG-IUS alone or in combination with other treatments. Fifty-six women (28%) were using LNG-IUS at 10 years. There were improvements over time in quality of life scores, with no evidence of differences in these or other outcomes between the two groups.

Conclusions

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

Female, menorrhagia, cohort studies, quality of life, hysterectomy, endometrial ablation techniques, primary health care

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 to inform patient and clinical decision-making. 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 medical treatments for women with HMB can be initiated in primary care with low subsequent rates of surgery and improvement in quality of life ten years later.

Introduction

Heavy menstrual bleeding (HMB) is a common problem that can significantly affect women's lives until menopause. Whilst diagnostic definitions using menstrual blood loss exist, it is the impact on a women'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 intra-uterine 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, NSAIDs, combined hormonal contraception, oral progestogens).[1] 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 GP and women).[3] Women's eligibility for the original trial, and their clinical assessment consistent with current NICE guidance, are detailed in the Supplementary appendix. 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 two years follow up.[3] By five years of 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.

There is no available research on medical treatment of HMB in the longer term in primary care, beyond the five-year data from the ECLIPSE trial[5]. While 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.

Methods

The ECLIPSE trial ended from a regulatory perspective at five years follow-up.[5] However, we continued data collection for this prospective observational study to ten 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.[3, 5] Women could subsequently swap or cease their allocated treatment. We aimed to collect 10-year data from 276 women, equating to 48% of the 571 women originally randomised (**see Figure 1 below**). This target anticipated further loss to follow-up due to the length of time elapsed since previous contact at two or five years, relocation, non-completion of questionnaire, or death. The process of recontacting and reconsenting participants is described in the Supplementary Appendix.

All data were collected directly by questionnaire (paper or via link to online form). The primary outcomes were use of treatments for HMB, and 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.[6] The patient-reported, condition-specific Menorrhagia Multi-Attribute Scale (MMAS)(4) at two years' 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, we planned manual extraction of data on surgical interventions and medical treatments for HMB from patients' GP records. Twenty-five women from 16 practices re-confirmed consent to this at 10 years. Their self-completed questionnaire data were independently compared by two researchers with their GP recorded data for completeness and accuracy, which was assessed as very high. Subsequent data extraction from GP

records was thus deemed unnecessary unless questionnaire data were missing. However, due to Covid-19 pandemic restrictions no further GP record extraction was performed.

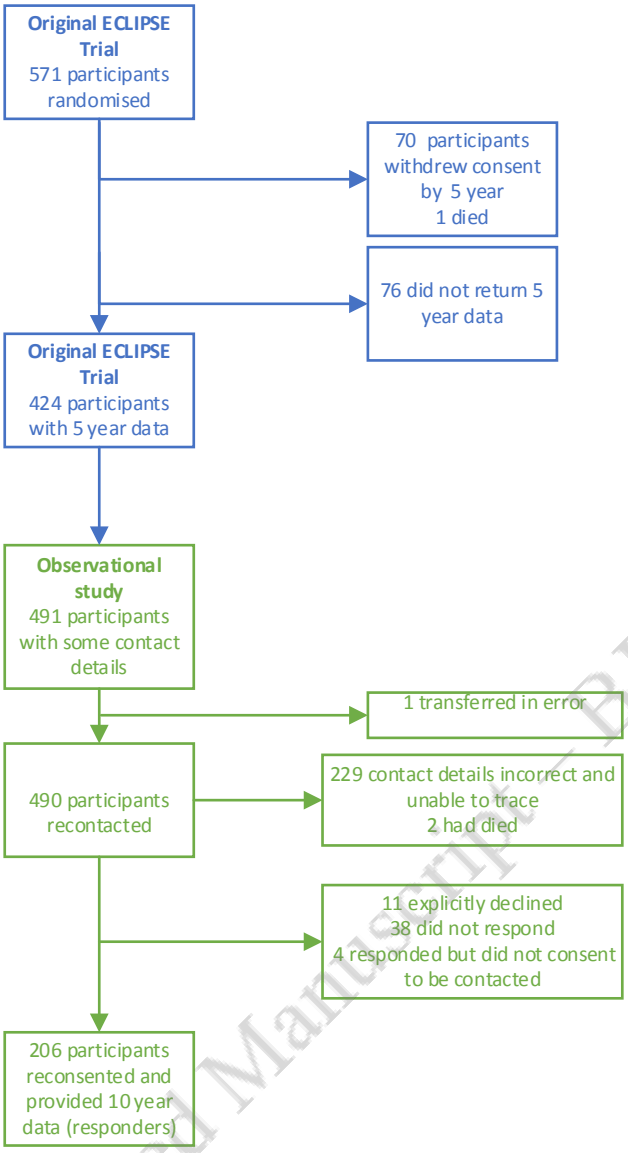
Characteristics of women completing 10 years follow up were compared to all other women in the original trial cohort (those declining when re-contacted or not responding to the re-contact invitation). Proportions of women of different ethnicity, HMB presentations, and randomised to different types of treatment were compared using Chi-squared test. Age in years, body-mass index, blood pressure and questionnaires scores (SF-36, EQ-5D, MMAS, SAQ) in the groups were compared using either Student's t-test for normally distributed variables or Mann-Whitney test otherwise. Imputation methods for data missing from the SF-36 and SAQ are described in the Supplementary Appendix.

The responding cohort of women at 10 years was divided into two subgroups according to their initial randomised treatment allocation. Characteristics and questionnaire scores at baseline and at 10 years of follow-up were compared using the same approach as above. Changes between baseline and 10-year follow up were assessed using paired t-test, whereas changes between groups were examined using an unpaired t-test. To compare surgical intervention rates in women allocated to different treatments we used Log-rank test for equality of survival functions and presented the estimates using Kaplan-Meier survival plots

Results

The flow 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 re-consent and returned completed 10-year follow-up data by 31 March 2020 (200 by mail, 6 online).

Figure 1 Flow of participants from the original ECLIPSE trial to observational study



Note: *Attempts to contact women after 23 March 2020 were curtailed due to the Covid-19 pandemic. See Supplementary Appendix.*

The baseline (prior to randomisation) characteristics of responders and those that were not followed-up are presented in **Table 1**. Responders were very similar to those women not followed up, with average age of 41.9 and 41.1 years, respectively, and did not differ clinically in their initial symptoms and presentations of HMB.

Table 1 Characteristics and questionnaire scores at baseline (prior to randomisation in original trial) between responders and women not followed up at 10 years.

Characteristic	All women followed up at 10 years n=206	All women not followed up N=365
Age at start, years		
Mean (SD) age	41.9 (4.9)	41.1 (5.4)
Age≥35	188 (91%)	324 (89%)
Ethnicity		
White	178 (86%)	293 (80%)
Asian	11 (5%)	40 (11%)
Black	9 (4%)	21 (6%)
Other	8 (4%)	11 (3%)
Body-mass index (kg/m^2)		
Mean (SD)	29.4 (6.4)	29.1 (6.4)
BMI≥25	146 (71%)	255 (70%)
Mean (SD) systolic blood pressure	129.7 (17.0)	128.5 (16.3)
Mean (SD) diastolic blood pressure	78.8 (10.2)	78.7 (10.5)
Presentation to primary care for HMB		
Initial	157 (76%)	279 (76%)
Subsequent	49 (24%)	86 (24%)
Duration of HMB more than a year	164 (80%)	296 (81%)
Menstrual pain	151 (73%)	273 (75%)
Contraception requirement	35 (17%)	75 (21%)
Copper or non-hormonal coil	7 (3%)	12 (3%)
Treatment at randomisation		
LNG-IUS	110 (53%)	175 (48%)
Usual medical treatments	96 (47%)	190 (52%)
Questionnaire scores (mean (SD, n))		
SF36		
Physical functioning	82.5 (19.4, 205)	76.2 (24.6, 339)
Physical role	71.7 (24.3, 205)	69.6 (26.2, 340)
Emotional role	72.0 (24.9, 204)	70.2 (26.6, 339)
Social functioning	65.7 (23.7, 205)	61.9 (26.0, 342)
Mental health	60.7 (19.6, 205)	59.1 (19.5, 340)
Energy and vitality	40.8 (21.9, 205)	40.7 (20.9, 340)
Pain	48.5 (22.6, 205)	45.6 (22.3, 342)
Perception of general health	62.2 (21.8, 205)	60.2 (21.7, 342)
EQ-5D		
Descriptive system	0.769 (0.228, 206)	0.714 (0.276, 340)
EQ-5D visual-analogue scale	71.6 (18.9, 185)	69.0 (19.7, 311)
Sexual Activity Questionnaire		
Pleasure	10.5 (5.0, 166)	11.1 (4.9, 248)
Discomfort	4.8 (1.4, 166)	4.5 (1.7, 248)
Menorrhagia Multi-Attribute Score	42.8 (19.4, 206)	39.7 (21.8, 206)

Note: If information was partially missing but over half of questions in a domain were answered, the average score of the responses was used, otherwise were classed as missing. The mean scores and number of contributing participants are slightly different to the original ECLIPSE Trial because of this method.

Allocation to different treatments was balanced across both groups of women: 110 of 206 (53%) responders and 175 of 365 (48%) of women not followed up were allocated to LNG-IUS. Responders and those not followed up also had similar baseline scores for SF36, EQ-5D and SAQ, with no domains showing a statistically significant difference (**Table 1**). Average scores at baseline for MMAS were slightly higher for women responding at 10 years (42.8 vs. 39.7), and the difference was not statistically significant.

The 206 responders had a mean age at response to the 10 year follow-up of 53.7 years (SD 5.1 years) and 178 (86%) were of white ethnicity. Amongst these, 110 were originally allocated to the LNG-IUS and 96 were allocated to other usual medical treatment. At the time of completing the 10-year follow up questionnaire, 106 (51%) women had reached menopause (defined for the responders as experienced no menstrual bleeding for at least one year) and 34 (17%) had had a hysterectomy, shown in

Table 2. Of those still menstruating, 12 women (6%) were still experiencing HMB and did not consider themselves menopausal.

Between 5 and 10 years of follow-up, a substantial proportion of women (89 (43%)) reported not taking treatments for HMB. However, 88 (43%) of women used LNG-IUS (67 women used only LNG-IUS, and 21 used LNG-IUS in combination with usual medical treatment). The proportions using LNG-IUS, alone or in combination, were higher for women initially allocated to LNG-IUS than to usual medical treatment: (58 of 110 women (53%) and 30 of 96 women (31%), respectively. Overall, 56 (28%) women reported they were using LNG-IUS at the time of response to the 10-year follow-up, (including 35% (38/110) of women originally allocated to LNG-IUS and 19% (18/96) of women originally allocated to medical treatments).

Table 2 shows the reported treatments by original randomised allocation. There were no statistically significant differences in treatments between the two randomised groups for any menopausal or treatment category.

Table 2 Menopausal status and reported treatments for heavy menstrual bleeding amongst all responders, and by original ECLIPSE trial allocations

	All responders (n=206)	Allocated to LNG-IUS (n=110)	Allocated to usual medical treatment (n=96)
Menopausal status			
Premenopausal	32 (16%)	16 (15%)	16 (17%)
Postmenopausal	106 (51%)	54 (49%)	52 (54%)
Undergone hysterectomy	34 (17%)	18 (16%)	16 (17%)
Perimenopausal or uncertain	32 (16%)	21 (19%)	11 (11%)
Missing	2 (1%)	1 (1%)	1 (1%)
Using menopausal hormone therapy	28 (14%)	16 (15%)	12 (13%)
Still experiencing heavy menstrual bleeding	12(6%)	6(5%)	6(6%)
Using LNG-IUS at response to 10-year follow-up	56 (28%)	38 (35%)	18 (19%)
Classes of treatments used between 5 and 10 years			
LNG-IUS	67 (33%)	47 (43%)	20 (21%)
Usual medical treatment	29 (14%)	10 (9%)	19 (20%)
LNG-IUS and usual medical treatment	21 (10%)	11 (10%)	10 (10%)
None	89 (43%)	42 (38%)	47 (49%)
Standard medical treatments used between 5 and 10 years			
Tranexamic acid	24 (12%)	7 (6%)	17 (18%)
Mefenamic acid	6 (3%)	3 (3%)	3 (3%)
Norethisterone	13 (6%)	4 (4%)	9 (9%)
Desogestrel	3 (1%)	0	3 (3%)
Oral contraceptives	8 (4%)	3 (3%)	5 (5%)
Medroxyprogesterone acetate injection	1 (<1%)	1 (<1%)	0
Naproxen	1 (<1%)	0	1 (<1%)
Surgical intervention for heavy menstrual bleeding			
Hysterectomy	34 (17%)	18 (16%)	16 (17%)
Endometrial ablation	26 (13%)	10 (9%)	16 (17%)

Table 3 reports the distributions of SF-36, EQ-5D and SAQ scores, for all responders and by the original randomized allocation, at 10-year after randomisation. There were no statistically significant differences between the randomized groups in any domain of the three questionnaires. Only 13 respondents, 12 of whom described their bleeding as heavy, completed the MMAS questionnaire, so distributions were not calculated, nor groups compared. The SAQ was completed by 116 of the 206 responding women, indicating at least 56% of women were sexually active.

Table 3 Questionnaire scores at 10 years amongst all responders, and by original ECLIPSE trial allocations

	All responders mean (SD, n)	Allocated to LNG-IUS mean (SD, n)	Allocated to usual medical treatment mean (SD, n)
SF-36			
Physical functioning	80.2 (26.2, 205)	81.4 (24.9, 110)	78.8 (27.7, 95)
Physical role	78.4 (28.6, 204)	80.1 (26.2, 109)	76.4 (31.1, 95)
Emotional role	79.4 (27.5, 204)	79.3 (26.4, 109)	79.5 (28.9, 95)
Social functioning	74.7 (25.8, 206)	75.5 (25.2, 110)	73.8 (26.6, 96)
Mental health	68.6 (21.5, 205)	68.1 (21.1, 110)	69.2 (22.0, 95)
Energy and vitality	48.9 (10.2, 205)	48.3 (8.8, 110)	49.5 (11.6, 95)
Pain	63.4 (24.8, 206)	64.3 (23.9, 110)	62.4 (25.9, 96)
Perception of general health	55.4 (9.6, 206)	55.9 (10.3, 110)	54.9 (8.7, 95)
EQ-5D			
Descriptive system	0.748 (0.266, 204)	0.757 (0.249, 110)	0.736 (0.286, 94)
Visual analogue scale	73.4 (20.7, 176)	74.9 (19.8, 93)	71.8 (21.6, 83)
Sexual Activity Questionnaire			
Pleasure	11.2 (4.6, 116)	11.5 (4.6, 62)	10.9 (4.6, 54)
Discomfort	2.01 (1.99, 116)	2.19 (2.09, 62)	1.80 (1.87, 54)

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 the allocation groups, but no changes were seen within the pleasure domain.

Table 4 Questionnaire scores at baseline and 10 years of follow-up

	Baseline scores for responders		10-year follow-up		Difference between groups over 10 years Mean (95% CI, p-value)	Change within group Mean (95%CI, p-value)	
	LNG-IUS	Usual medical treatment	LNG-IUS	Usual medical treatment		LNG-IUS	Usual medical treatment
SF36							
Physical functioning	84.0 (81.5 to 86.5)	80.7 (77.8 to 83.6)	81.2 (78.2 to 84.2)	78.8 (75.5 to 82.1)	-0.9 (-4.4 to 2.6), 0.786	-2.8 (-5.7 to 0.2), 0.220	-1.9 (-4.9 to 1.1), 0.409
Physical role	74.0 (71.0 to 76.9)	69.1 (65.9 to 72.2)	79.9 (76.8 to 83.0)	76.4 (72.9 to 79.9)	-1.3 (-5.4 to 2.8), 0.760	6.0 (2.7 to 9.3), 0.038	7.3 (3.7 to 10.9), 0.034
Emotional role	72.4 (69.4 to 75.5)	71.2 (68.1 to 74.4)	79.8 (76.8 to 82.9)	79.5 (76.1 to 82.8)	-0.8 (-4.9 to 3.2), 0.844	7.4 (4.2 to 10.6), 0.007	8.2 (4.6 to 11.9), 0.018
Social functioning	67.2 (64.4 to 70.0)	64.1 (60.9 to 67.3)	75.2 (72.2 to 78.3)	73.8 (70.6 to 77.1)	-1.7 (-5.6 to 2.2), 0.661	8.0 (5.0 to 11.0), <0.001	9.8 (6.2 to 13.3), 0.004
Mental health	61.7 (59.0 to 64.4)	60.0 (57.3 to 62.8)	68.1 (65.3 to 70.9)	69.2 (66.2 to 72.1)	-2.8 (-6.1 to 0.5), 0.331	6.3 (3.7 to 9.0), <0.001	9.1 (6.2 to 12.1), <0.001
Energy and vitality	41.6 (38.8 to 44.4)	40.0 (37.0 to 43.0)	48.3 (46.5 to 50.1)	49.5 (47.4 to 51.7)	-2.8 (-6.4 to 0.7), 0.392	6.7 (3.8 to 9.6), 0.003	9.5 (6.5 to 12.6), <0.001
Pain	49.0 (46.1 to 51.9)	47.9 (44.9 to 50.9)	64.1 (61.2 to 67.1)	62.4 (59.2 to 65.6)	0.7 (-3.2 to 4.5), 0.866	15.1 (12.0 to 18.3), <0.001	14.5 (11.1 to 17.8), <0.001

Perception of general health	63.5 (60.7 to 66.3)	60.7 (57.7 to 63.6)	56.0 (54.0 to 57.9)	54.9 (53.0 to 56.7)	-1.8 (-5.2 to 1.7), 0.564	-7.5 (-10.4 to -4.7), <0.001	-5.8 (-8.7 to -2.8), 0.011
EQ-5D							
Descriptive system	0.78 (0.50 to 1.07)	0.75 (0.44 to 1.06)	0.76 (0.46 to 1.06)	0.74 (0.40 to 1.07)	-0.01 (-0.39 to 0.37), 0.782	-0.03 (-0.33 to 0.28), 0.270	-0.02 (-0.36 to 0.33), 0.607
Visual-analogue scale	73.5 (70.7 to 76.3)	70.3 (67.3 to 73.3)	76.2 (73.5 to 78.9)	72.3 (69.3 to 75.4)	0.7 (-2.9 to 4.3), 0.832	2.8 (-0.2 to 5.7), 0.214	2.0 (-1.1 to 5.2), 0.442
Sexual Activity Questionnaire							
Pleasure	11.8 (10.3 to 13.3)	10.4 (8.6 to 12.1)	11.3 (9.7 to 12.8)	10.9 (9.3 to 12.5)	-1.1 (-3.2 to 1.0), 0.323	-0.5 (-2.3 to 1.2), 0.487	0.6 (-1.2 to 2.3), 0.482
Discomfort	4.6 (3.8 to 5.5)	5.0 (4.1 to 5.8)	2.3 (1.3 to 3.4)	1.7 (0.8 to 2.7)	0.9 (-0.5 to 2.3), 0.075	-2.3 (-3.5 to -1.1), <0.001	-3.2 (-4.4 to -2.1), <0.001

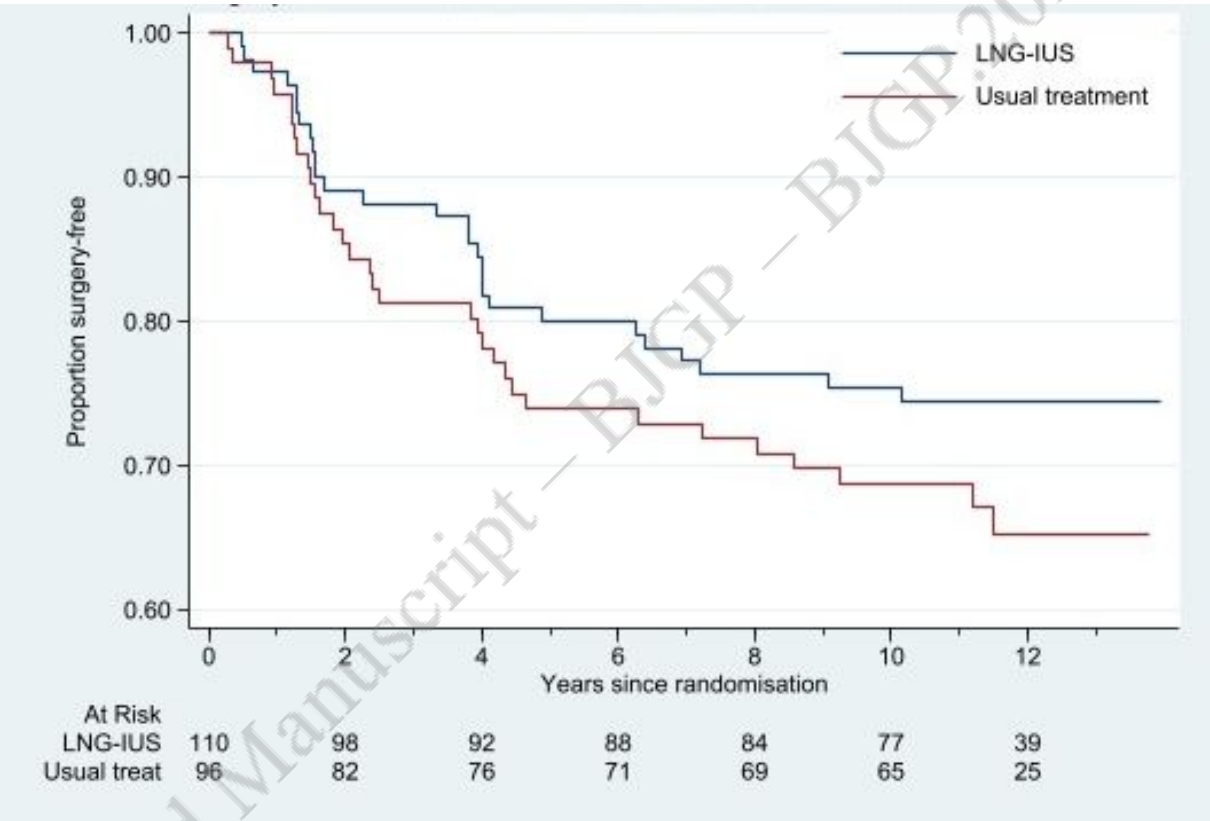
Note: Scores are only calculated for women who provided both baseline and 10-year data, so the baseline scores are slightly different from those reported for the original ECLIPSE trial and in **Table 3**, where all scores are reported.

Surgical interventions

Over the 10-year follow-up period, there were 60 of 206 (29%) women who had had surgical intervention, including hysterectomy (34 (16.5%)) or endometrial ablation (26 (12.6%)), (

Table 2). No woman had both procedures and no woman 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 of 110 women, 25%) compared to those allocated to standard medical treatment (32 of 96, 33%) 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%CI 0.44 – 1.21, p=0.22).

Figure 2 Surgery-free time for all responders by original ECLIPSE trial allocations



Discussion

Principal Findings

This study shows medical treatments for women with heavy menstrual bleeding can be initiated in primary care with improvement in quality of life and high likelihood of avoiding surgery ten years later. We have found among women, typically presenting with HMB in their early forties, 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 (43%) 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 five (20%) and two (10%) years after commencing treatment in primary care.[3,5] 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.[3,5] We achieved responses from 206 women, 36% of the original trial population and 42% of those we could potentially re-contact after 10 years. Whilst this was lower than anticipated due to difficulties during the height of the Covid-19 pandemic, such long-term data for women with HMB 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 generalizability of the trajectories reported. 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 further research with women from minority communities is needed as HMB experiences may differ, especially given the higher prevalence of fibroids in Black women. [7]

Given the proportion of participants who had changed or ceased their original allocated treatments by five years, it was anticipated 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 expectedly stopped having periods, either due to the menopause, or surgical treatment, meaning few women were able to report on the original primary outcome measure, the MMAS. Nevertheless, we have been able to illustrate for the first time the proportion of women progressing to surgical intervention by initial medical treatment.

We originally proposed 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 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 was most realistically achievable. Participating women's qualitative experiences of HMB and influences on their treatment over time will be reported separately.

Relation to other studies

This study is the first to report outcomes a decade after commencing medical treatment for HMB in primary care. Evidence from a secondary care trial comparing LNG-IUS with hysterectomy followed 119 women allocated LNG-IUS, reporting 55 (46%) had had a hysterectomy, 44 (37%) were still using LNG-IUS, one had had endometrial ablation and 18 were not using LNG-IUS after ten years.[8] The higher rate of hysterectomies can be attributed to women's recruitment from a hysterectomy waiting list. As our starting point was initial medical treatment, we had too few women who had had endometrial ablation to determine the rate of subsequent procedures: previous evidence suggests around 20% of women need further surgery.[9]

There are no recent UK data to suggest a change in patterns of treatments for HMB. Drug utilisation data in Denmark between1996-2017 showed a large increase in use of LNG-IUS, (from 2.3 to 32 users per 1000 person-years) and decline in use of oral tranexamic acid (from 11.3 to 6.3 per 1000 person-years) for women aged 20-54 years. Use of combined hormonal contraceptives remained stable, while use of cyclical oral progestogens decreased.[10] Dutch data between 2004-2013 show progestogen prescriptions also declining over time, though LNG-IUS was used in less than 2.5% of cases [11].

Implications for practice

The original ECLIPSE trial recruited women from the general population who had HMB that was affecting their lives, who chose to present to their GP with this problem; and who were clinically assessed as appropriate for, and who wanted to have medical treatment. This assessment and the range of medical treatments used (LNG-IUS or other standard medical treatments) reflected real-life practice and remains the range of choices available to women of any age and their GP in the community setting, according to women's individual needs and preferences. This is consistent with current updated NICE guidance for initial management of HMB [(1)].

The sustained low rates of progression to surgical intervention observed, and general improvement in quality of life, ten 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 ten-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. On-going 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 five years that they may continue to benefit and avoid surgery.

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 ten 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.

Acknowledgements

Funding

National Institute of Health Research (NIHR) Health Technology Assessment Programme (HTA 15/143/01)

Contributions of Authors

Joe Kai (GP & Professor of Primary Care): conceptualization, writing (original draft), writing (review and editing), project supervision, investigation, analysis, funding acquisition.

Brittany Dutton (Research Assistant): fieldwork, data curation, writing (review and editing), investigation, project administration.

Yana Vinogradova (Senior Research Fellow): statistical analysis, data curation, formal analysis, writing (original draft, review and editing).

Nicholas Hilken (Senior Database Developer): data curation, writing (review and editing)

Janesh Gupta (Professor of Obstetrics and Gynaecology): conceptualization, writing (review and editing), investigation, funding acquisition.

Jane Daniels (Professor of Clinical Trials): conceptualization, writing (original draft), writing (review and editing), project administration, investigation, funding acquisition.

Acknowledgements

The Authors acknowledge the contribution of the ECLIPSE Trial Collaboration, listed in Health Technology Assessment (2015) 15(88). The authors dedicate this project to the memory of Professor Helen Pattison (1954-2021).

We thank all women participating in the study for their time and commitment to this research. We thank our two PPI advisors Claire Mann and Farah Jamil for their valuable contributions, advice and support throughout the study; and Pamela Pepper for her administrative support and help with referencing. We thank three anonymous peer reviewers of the full study report, and BJGP reviewers (<names> if deemed appropriate) for their helpful comments.

Data sharing

Data requests for 10-year data should be submitted to the corresponding author for consideration. Access to available anonymised data may be grant following review.
Data requests for the original ECLIPSE trial dataset should be submitted to bctudatashare@bham.ac.uk.

References

1. National Institute for Health Care and Excellence. Heavy menstrual bleeding: assessment and management. NICE guideline [NG88]. Last updated: 31 March 2020. Available at: https://wwwniceorguk/guidance/ng88 [Accessed 08 April 2021]. 2018.
2. Janssen CAH, Scholten PC, Heintz APM. Reconsidering menorrhagia in gynecological practice. Is a 30-year-old definition still valid?
Eur J Obstet Gynecol Reprod Biol 1998;78(1):69-72.
3. Gupta J, Kai J, Middleton L, Pattison H, Gray R, Daniels J, et al. Levonorgestrel intrauterine system versus medical therapy for menorrhagia. N Engl J Med. 2013;368(2):128-37.
4. Shaw RW, Brickley MR, Evans L, Edwards MJ. Perceptions of women on the impact of menorrhagia on their health using multi-attribute utility assessment. Br J Obstet Gynaecol 1998;105(11):1155-9.
5. Kai J, Middleton L, Daniels J, Pattison H, Tryposkiadis K, Gupta J. Usual medical treatments or levonorgestrel-IUS for women with heavy menstrual bleeding: long-term randomised pragmatic trial in primary care. Br J Gen Pract 2016;66(653):e861-e70.
6. Thirlaway K, Fallowfield L, Cuzick J. The Sexual Activity Questionnaire: a measure of women's sexual functioning. Qual Life Res. 1996;5(1):81-90.
7. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol. 2003; 188(1):100-7. doi: 10.1067/mob.2003.99.
8. Heliövaara-Peippo S, Hurskainen R, Teperi J, Aalto A-M, Grénman S, Halmesmäki K, et al. Quality of life and costs of levonorgestrel-releasing intrauterine system or hysterectomy in the treatment of menorrhagia: a 10-year randomized controlled trial. Am J Obstet Gynecol. 2013;209(6):535.e1-.e14.
9. Bhattacharya S, Middleton LJ, Tsourapas A, Lee AJ, Champaneria R, Daniels JP, et al. Hysterectomy, endometrial ablation and Mirena for heavy menstrual bleeding: a systematic review of clinical effectiveness and cost-effectiveness analysis. Health technology assessment (Winchester, England). 2011;15(19):iii-252.
10. Meaidi A, Kuhr Skals R, Alexander Gerds T, Lidegaard O, Torp-Pedersen C. Decline in Danish use of oral tranexamic acid with increasing use of the levonorgestrel-releasing intrauterine system: a nationwide drug utilization study. Contraception. 2020;101(5):321-6.s
11. Van den Brink MJ, Saaltink AL, Groenhof F, Incidence and treatment of heavy menstrual bleeding in general practice. Fam Pract. 2017; 34(6):673-678. doi: 10.1093/fampra/cmx050
12. Ware J, Kosinski M, Gandek B. SF-36 Health Survey: Manual & Interpretation Guide. Lincoln, RI: QualityMetric Incorporated. 1993.