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Medical therapies for heavy menstrual bleeding in women with uterine fibroids: a retrospective analysis of a large commercially insured population in the USA

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Abstract

Objectives—To report patterns and patient characteristics associated with initiation of and persistence with medical therapies for uterine fibroid-related heavy menstrual bleeding.

Design—Retrospective cohort study.

Setting—US commercial insurance claims database.

Population—41 561 women aged 18–54 years with uterine fibroids and heavy menstrual bleeding who initiated medical therapies from January 2000 through December 2013.

Metho—Multinomial logistic regression was used to assess patient characteristics associated with initiation and persistence. Cox proportional hazards regression was used on propensity score-matched cohorts to examine change from index medication.

Main outcomes measures—Initiation of and persistence with four first-line medical therapies: short- and long-acting reversible contraceptive steroids, leuprolide acetate, and tranexamic acid.

Results—Most women (79.4%) took short-acting reversible contraceptive steroids as first-line therapy (*index medication*), whereas 9.5%, 8.5%, and 2.7% used long-acting reversible contraceptive steroids, leuprolide acetate, and tranexamic acid, respectively. During follow-up, 16 594 women (39.9%) switched to nonindex medication (18.4%) or procedural treatment (81.6%).

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Disclosure of interests

Xiaoxi Yao, Bijan J. Borah, and Herbert C. Heien have no financial disclosures or potential conflicts to report.

The ICMJE disclosure forms are available as online supporting information.

Contribution to authorship

Study Concept and design: Drs Borah, Stewart, and Laughlin-Tommaso. Acquisition, analysis of data: Dr Yao, Heien. Interpretation of data: All authors. Drafting of the manuscript: Drs Yao and Borah. Critical revision of the manuscript for important intellectual content: All authors.

Data access and responsibility

Xiaoxi Yao had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors take the responsibility for the published article.

In comparison with women taking short-acting steroids, those receiving long-acting steroids were less likely to switch [hazard ratio (HR) 0.84, 95% CI 0.79–0.91], whereas women taking leuprolide acetate (HR 2.44, 95% CI 2.27–2.62) or tranexamic acid (HR 1.44, 95% CI 1.26–1.65) were more likely to switch. Older age, emergency department visits, anaemia, and inflammatory disease diagnoses at baseline were associated with increased probability of discontinuing the index medication or switching to another therapy.

Conclusions—Women with uterine fibroid-related heavy menstrual bleeding were more likely to persist with their initial therapy of long-acting reversible contraceptive steroid compared with other medical options.

Keywords

Heavy menstrual bleeding; leuprolide acetate; long-acting reversible contraceptive steroid; short-acting reversible contraceptive steroid; tranexamic acid; uterine fibroids or leiomyomas

Introduction

Uterine fibroids (UFs), also called *leiomyomas*, are common benign gynaecological tumours, with a cumulative incidence of nearly 70% in white women and more than 80% in black women by age 50 years.[1] Approximately 200 000 of the 600 000 hysterectomies performed annually in the USA have a discharge diagnosis of UF.[2] The annual direct cost of treating UFs was estimated at $3.2–9.4 billion dollars (2010 dollars) in the USA.[3,4]

One of the primary symptoms associated with UF is heavy menstrual bleeding (HMB), which can impair quality of life[5–7] and may lead to other medical conditions, such as iron-deficiency anaemia.[8] Although medical therapy is the first-line treatment of HMB, little evidence is available regarding the specific types of current medical therapies and their clinical use for HMB in women with UF. A 2011 report from the U.S. Agency for Healthcare Research and Quality (AHRQ) concludes that the evidence on comparative effectiveness of UF therapies is insufficient, making healthcare and therapeutic decisions difficult for both patients and physicians.[9] Determining the relative effectiveness of non-procedural UF therapies is one of the two highest priority questions identified by the AHRQ evidence-based report.[9] Before conducting any comparative effectiveness study, a good understanding of how these medical therapies are used in practice is needed. Furthermore, in the absence of comparative effectiveness data, patient persistence and adherence may be important to consider when selecting treatment. Currently, there are few data on the utilisation patterns of these medications or associated patient characteristics.

The present study aimed to examine the utilisation patterns of UF medications in women with UF and HMB. We specifically examined the patient characteristics associated with initiation of and persistence with the initial medical therapy. Knowledge of these patient characteristics will help patients and their care providers to optimise their choices for first-line medical therapy and improve patient satisfaction.

Methods

Data source

We conducted a retrospective analysis of administrative claims data from the Optum Labs Data Warehouse. This data warehouse contains longitudinal health information of more than 100 million privately insured and Medicare Advantage enrollees from a large US insurance company; this database contains longitudinal healthcare claims data for the past 20 years from geographically diverse US regions, with the South and Midwest having the greatest representation.[10]

The health plans contributing to the database provide full insurance coverage for inpatient, outpatient, and pharmacy services. Medical claims include *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* (ICD-9-CM) diagnosis codes and the procedure codes of the *International Classification of Diseases*, *Ninth Revision*, Current Procedural Terminology Fourth Edition, and Healthcare Common Procedure Coding Systems. Data of pharmacy claims include fill date, generic name, brand names, and days of supply for each drug. Socio-economic characteristics include income and race/ethnicity.[11] All study data were accessed through techniques compliant with the Health Insurance Portability and Accountability Act of 1996. Because the present study involved evaluation of pre-existing, de-identified data, the Mayo Clinic Institutional Review Board deemed it exempt from board approval.

Study population

The study population contained women aged 18–54 years who had diagnoses for both UF (ICD-9-CM 218.x, 219.x, and 654.1x) and HMB (ICD-9-CM 626.2 and 627.0) and who initiated medical therapies from 1 January 2000 through 31 December 2013. See Supporting Information Tables S6 and S7 for detailed description of the codes. Four medication classes were commonly used to treat UF-related HMB in the USA[12–16] and were included in the study: short-acting reversible contraceptive steroids (SARCs), including oral, transdermal and vaginal ring contraceptives; long-acting reversible contraceptive steroids (LARCs), including steroidal implants, depot medroxyprogesterone acetate, and levonorgestrel-releasing intrauterine system (LNG-IUS); leuprolide acetate (LA), a long-acting gonadotropin-releasing hormone agonists; and tranexamic acid (TA), an oral antifibrinolytic agent.

The first filled prescription among any of the study drugs and from 2000 through 2013 was defined as *index medication*, which determined a patient's medication cohort. The fill date of the index medication was defined as *index date*. Women in the study were required to have at least 12 months of continuous enrollment in both medical and drug insurance plans before the index date (defined as *baseline period*). In addition, women were required to have at least one UF diagnosis and one HMB diagnosis (primary or secondary) at baseline, to increase the likelihood that the medical therapies were used as the primary therapy for UF-related HMB. We also required at least 6-month continuous enrollment in medical and pharmacy plans after the index date. To ensure that the sample included only initial treatment, we excluded women who had medications (LA and TA) or procedural therapies

[i.e. endometrial ablation, magnetic resonance-guided focused ultrasonography (MRgFUS), uterine artery embolisation, hysterectomy, and myomectomy] used primarily for UF or HMB during any time before the index date. Women with uterine cancer (ICD-9-CM 179 and 182.x) at any time were also excluded.

Outcomes

Women were monitored from the index date until the earliest of the following dates: the end of enrollment in the health plans, the end of the study period, or the time of switching from or discontinuing the index medication. *Switching* therapies was defined as changing the index medication to a different medication class (a nonindex medication) or undergoing a procedural therapy while receiving the index medication or within 90 days of stopping the index medication. The 90-day grace period allows the time needed for a woman to discuss with her physicians the treatment options or to schedule procedures. *Discontinuation* was defined as not refilling a prescription or not having any residual supply of the index medication. For patients on LARC, either renewing or removing LARC was considered discontinuation. *Date of discontinuation* was defined as the expected completion of the last prescribed dose for that medication (e.g. 90^{th} day for a 90-day supply of pills, 5 years after placement of intrauterine device). Supporting Information Figure S1 provides a schematic depiction of these time intervals. *Persistence* was defined as the patient's duration of the index medication (i.e. until she switched or discontinued the index medication).[17] *Adherence* to a specific medication was defined as 80% or higher proportion of days covered during the time when a patient was taking the index medication.

Independent variables

Demographic and socio-economic characteristics at the index date (i.e. age, race/ethnicity, household income, and residence region), baseline comorbidities, Charlson-Deyo comorbidity index,[18] and baseline health care utilisation were independent variables. We measured baseline UF and all-cause healthcare utilisation by calculating the number of UF-related inpatient, emergency department, and outpatient visits. *UF-related health care utilisation* was defined as having a primary or secondary diagnosis of UF in the corresponding claim. Measured comorbidities covered a wide range of diseases related to UF, including pelvic pain, dyspareunia, endometriosis, and benign neoplasm of the uterus or ovary. See Suppporting Information Table S1 for the detailed list. Because the aim of the study was to assess whether and to what extent certain patient demographic, socio-economic and clinical characteristics are associated with the utilisation patterns, we did not intend to build a predictive model. Therefore, we included covariates available in the database, which are thought to be associated with different utilisation patterns based on our clinical experience.

Statistical methods

Descriptive analyses were used to characterise demographic and socio-economic characteristics, baseline comorbidities, baseline health care utilisation, and treatment during follow up, stratified by index medication. Continuous variables were compared between groups using nonparametric Kruskal–Wallis test, and categorical variables were assessed using Chi-square test. We conducted two multinomial logistic regression analyses. The first

assessed factors associated with initiation of any of the four index medications; the second assessed factors associated with women continuing the index medication, discontinuing it, or switching to other therapies. We chose multinomial logistic regression, which fits maximum-likelihood multinomial logit model, because the outcomes are not binary, rather they are multi-categorical variables. SARC was used as the reference category in the first regression, and continuing index medication was used as the reference category in the second regression. The primary outcome of switching from the index medication was also analysed as a time-to-event variable. To balance the baseline covariates, we first used one-to-one propensity score matching with a caliper of 0.001 and without replacement to match each of three drug cohorts (LARC, LA, and TA) to the SARC cohort[19] because SARC was the most commonly used first-line medical therapy in our sample. Secondly, a Cox proportional hazards regression model was used to determine which cohort was most likely to switch compared with the SARC cohort. Because TA was approved by the U.S. Food and Drug Administration in November 2009, the TA cohort had a relatively short follow up, and we limited the study period to 3 years for the survival analysis comparing TA and SARC. For other medical therapies, we limited the survival analysis to 5 years because only 18% of the cohort had continuous enrollment for 5 years.

All analyses were conducted with the statistical software packages SAS version 9.3 (SAS Institute Inc.) and STATA version 13.1 (Stata Corp.). The level of statistical significance was set at $P < 0.05$.

Results

Our study population contained 41 561 women, with 33 000 (79.4%) receiving SARC as their index medication; 3928 (9.5%), LARC; 3525 (8.5%), LA; and 1108 (2.7%), TA. Supporting Information Figure S2 documents how the current study size was derived. The women had a median [interquartile range (IQR) follow up of 2.3 (1.2–4.2) years and continued taking the index medication for a median (IQR) period of 0.3 (0.1–1.1) years.

Because of the space constraints, Tables 1, 2 and 4 report only key characteristic (complete tables can be found in Supporting Information Tables S1–S3). Table 1 outlines patient characteristics for the overall sample and for each medication cohort. The mean (SD) age of the whole cohort was 42.7 (6.7) years; the TA cohort was older (mean age, 44.0 years) than all other cohorts but the absolute age difference among groups was small. The majority of the study sample (61.3%) were white and 42.8% of them were from the US South. Because most of the study population was in the SARC cohort, the characteristics of SARC were similar to the entire study population. Compared with the SARC cohort, a higher percentage of LARC, LA, and TA cohorts were black (12.8 versus 17.1%, 18.5%, and 24.4%), had an annual household income less than $40,000 (13.7 versus 16.3%, 14.9%, and 15.0%), and had anaemia (26.3 versus 31.5%, 47.9%, and 41.5%), respectively. The LA cohort also had the highest prevalence of inflammatory diseases (5.3 versus 3.2% in the study population) and endometriosis (8.9 versus 4.7%). In contrast, the TA cohort had a lower prevalence of inflammatory diseases (1.5%) and endometriosis (3.2%). Compared with the study population, the LA cohort had the highest baseline number of UF-related outpatient visits

(2.2 versus 1.5), and the LARC cohort had the highest number of all-cause outpatient visits (14.0 versus 12.8) at baseline.

Patient characteristics were associated with which first-line medication was used (Tables 2 and S2). Women with a high income (>$100,000 versus <$40,000) were less likely to receive LARC [relative risk ratio (RRR) 0.83, 95% CI 0.73–0.93] or LA (RRR 0.84, 95% CI 0.73–0.96) than SARC, but they were more likely to receive TA than SARC (RRR 1.57, 95% CI 1.27–1.95). Compared with black women, white women were less likely to receive any medication other than SARC. Certain baseline comorbidities also affected the use of first-line medical therapy: Having anaemia at baseline was significantly associated with medications other than SARC, with more than twice the likelihood of LA than SARC (RRR 2.27, 95% C (1.97–2.61).

During follow up, 39.9% of women switched to another therapy, 46.3% discontinued the index medication therapy without switching, and only 13.8% continued the index medication until the end of either health plan enrollment or study period (Table 3). LARC therapy had the highest percentage (36.9%) of continued use. The proportions of women who continued receiving the index medication at 3 months, 6 months, 1 year, 2 years, and 5 years were greatest for the LARC cohort (Supporting Information Table S4). At the end of 2 years of follow up, 42.4% of the women taking LARC continued taking the medication, compared with only 1.6% of LA, 23.6% of SARC, and 6.0% of TA. Virtually the entire LA cohort either switched (67.7%) therapies or discontinued (31.9%) the index therapy. Among the 16 594 women who switched therapies, only 3053 (18.4%) switched to a nonindex medication. The other women ultimately had a UF procedure: nearly half (45.7%) had hysterectomy; 24.1%, endometrial ablation; 8.5%, myomectomy; and 3.2%, uterine artery embolisation. The proportion of patients who adhered to treatment was 89.4, 54.7, 63.5, and 56.6% in the LARC, LA, SARC, and TA cohorts, respectively.

Supporting Information Figure S3 shows Kaplan–Meier survival curves that model time to medication switching. Figure S3-A shows all medications before propensity score matching. Figure S3-B through Figure S3-D show each of three comparisons after propensity matching between the relevant cohorts. Women using LARC were less likely to switch than were those taking SARC (HR 0.84, 95% CI 0.79–0.91). In contrast, women using LA (HR 2.44, 95% C (2.27–2.62) and TA (HR 1.44, 95% CI 1.26–1.65) were more likely to switch than were women taking SARC (Supporting Information Table S5).

Both clinical and nonclinical patient characteristics were associated with discontinuation or switching from the index medication (Tables 4 and S3). Compared with women aged 18–40 years, those aged 41–46 years and >46 years were more likely to discontinue the index medication (RRR 1.76, 95% CI 1.62–1.91) and to switch (RRR 1.46, 95% CI 1.34–1.58). Compared with white women, Asian (RRR 1.36, 95% CI 1.16–1.59), black (RRR 1.28, 95% CI 1.15–1.42), and Hispanic (RRR, 1.39, 95% CI 1.24–1.55) women were more likely to discontinue medication. Although the likelihood of switching was similar for black and Hispanic women compared with white women, Asian women were less likely to switch (RRR 0.80,, 95% CI 0.67–0.94). Women with higher income were less likely in general to discontinue or switch medication. Women from the Northeast USA were more likely to

discontinue the index medication (RRR 1.11,, 95% CI 1.01–1.23) but less likely to switch to other therapies (RRR 0.76, 95% CI 0.69–0.85) than were women from the Midwest. Baseline numbers of UF-related inpatient, outpatient, and emergency department visits were associated with an increased probability of switching to other therapies. Certain comorbidities at baseline also were related to increased likelihood of a medication switch or discontinuation, including anaemia (RRR 1.79, 95% CI 1.65–1.93 and RRR 1.24, 95% CI 1.15–1.34) and inflammatory diseases (RRR 1.29, 95% CI 1.05–1.58 and RRR 1.43, 95% CI 1.17–1.74, respectively.

Discussion

Main findings

In this large cohort of commercially insured women, short-acting reversible contraceptive steroids are the most widely used first-line treatment for uterine fibroid-related heavy menstrual bleeding. However, use of long-acting reversible contraceptive steroids is associated with significantly improved persistence with initial therapy. This is particularly notable as women utilising LARCs were more likely to be black and to have anaemia at baseline, factors indicative of more severe disease. Certain socio-demographic characteristics, comorbidities, and baseline health care utilisation were associated with the initiation, discontinuation and switch of therapies.

Strength and limitations

In this study, we monitored a large contemporary cohort of US women with UF-related HMB, using well-documented prescription and procedure data for an average of 3 years. The findings provided valuable evidence on the utilisation patterns of medical therapies for UF-related HMB.

However, we were not able to directly measure clinical outcomes (e.g. reduction in menstrual bleeding), clinical factors (i.e. size and location of fibroids), patient satisfaction or specific reasons for discontinuation or switching to other therapies. Another limitation of this approach is that LA in particular might be prescribed as a preoperative medication; women might have already decided to have a procedural therapy and the medication was used to improve surgical outcome. Therefore, for some women, particularly those in the LA cohort, switching to procedural therapies was not due to patient dissatisfaction or treatment failure of the first-line medication. To address this potential limitation, a sensitivity test was conducted including only the women who continued taking the index medication for at least 3 months, to minimise inclusion of preoperative use of the medications. The findings remained unchanged, validating the overall findings of the study.

Missing pharmacy claims should be rare in our database. Even when patients have to pay the entire amount out of pocket before their deductible requirement is met, as long as the drug is covered by the pharmacy benefit plan, patients still have the incentive to submit a claim so that such pharmacy expenses are counted towards the deductible. Moreover, the very fact that our study cohorts included patients who had an initial claim for the medications, implies that their treatments were likely to be covered by insurance, and we therefore should have

nearly complete data of their treatment during follow up when they stayed enrolled in the insurance.

Finally, the estimation of the duration of TA treatment might not be accurate. Physicians often prescribe TA with 5 days of supply or fewer, which has been standardised to a month's supply to reflect the menstruation cycle in this study. However, some women might allocate this prescription to 2 or 3 months when HMB occurs for fewer than 5 days per month.

Interpretation

Understanding the use, duration of use, associated patient characteristics and baseline comorbidities provides an important foundation for subsequent studies of UF-related HMB. Furthermore, understanding current medical therapies and then optimising strategies for symptom control may impact on hysterectomy rates in the USA. This is critical given the fact that of all surgical therapies for fibroids, hysterectomy still accounts for roughly three-quarters of all procedures.[20]There is also a group of women with fibroids who prefer non-interventional therapies; the fact that black women are more likely to prefer uterine-sparing treatments is important given that black women have more severe and earlier-onset disease.[21,22]

In this study, the finding that black women had an increased risk compared with white women of receiving LARC versus SARC as first-line therapy is intriguing. Although we don't have clinical outcomes data or data regarding symptoms and uterine anatomy, longer persistence of therapy in this high-risk group may be suggestive of superior clinical efficacy of LARCs for fibroid-related HMB, as is seen in idiopathic HMB. Alternatively, this increased persistence may be due to the differences in preferences of women or providers or the concomitant need for reliable contraceptions. Regarding persistence, women with low annual household income (<$40,000) were more likely to discontinue and switch therapies, which suggested potential financial barriers to long-term use of medical therapies. Certain baseline comorbidities (e.g. anaemias, inflammatory diseases) might have affected the perceived effectiveness and satisfaction with initial medical therapies and therefore might have increased the likelihood of discontinuing initial therapy and switching to other therapies.

Previous studies have found that LNG-IUS, a therapy in the LARC class, was superior to other medications for controlling HMB.[15,23–26] However, Mercorio et al.[16] found reduced effectiveness of LNG-IUS in UF-related HMB and a high expulsion rate (12%) among women with submucosal fibroids. In our study, we found that women continued taking LARC longer than any other medical therapy. The ease of medication adherence, as well as HMB control, might explain the longer duration on LARC compared with other medical therapies. In general, LARC therapy lasts 3–5 years unless women decided to remove the treatment device, whereas the other three medical therapies required women to regularly refill medications or receive an injection. LARC also reduced the adherence issue from the effectiveness equation, whereas only 55–64% of women taking SARC, LA, and TA adhered to the treatment (proportion of days covered, ≥80%).

Although it is obvious that LARC has a better continuation and/or higher adherence rate, the higher switching and discontinuation rates in other medication groups highlighted the importance of considering the expected persistence when selecting treatment, and the potential advantage of LARC in this aspect. The American College of Obstetricians and Gynecologists recommends that LARCs be used as first-line contraception for most women.[27] Our study suggests that when selecting the first-line medication to treat UF-related HMB, the better persistence and adherence associated with LARC need to be considered in addition to the benefit of avoiding unintended pregnancy.

Because our study used data from one of the largest commercial insurance company in the USA, the results can be generalisable to the commercially insured patients; however, the study results may not be generalisable to the patient population under the Medicaid program, which provides health insurance to low-income people in the USA. Another potential limitation is that there are many other characteristics that could influence patients' initiation, discontinuation, and switch, but are not available in healthcare claims databases, such as patients' value and preference, insurance benefits, and financial situations.

Conclusion

Overall, our study found that SARC is the most widely used class of medications for initial treatment of UF-related HMB. However, LARC is associated with better persistence with initial therapy. Treatment decisions—in particular, initiating, discontinuing, and switching medications—may be influenced by women's socio-demographic characteristics, comorbidities, and healthcare utilisation at baseline. Further investigation of LARC for women with UF-associated bleeding appears warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Details of ethics approval

As this study involved evaluation of pre-existing, de-identified data, the Mayo Clinic Institutional Review Board deemed it exempt from board approval. A statement to this effect is also provided in the methods section under the 'Data Source' subsection.

Abbreviations

HMB	heavy menstrual bleeding
HR	hazard ratio
ICD-9-CM	*International Classification of Diseases*, *Ninth Revision*, *Clinical Modification*
LA	leuprolide acetate
LARC	long-acting reversible contraceptive steroid
LNG-IUS	levonorgestrel-releasing intrauterine system
MRgFUS	magnetic resonance–guided focused ultrasonography
NIH	National Institutes of Health
RRR	relative risk ratio
SARC	short-acting reversible contraceptive steroid
TA	tranexamic acid
UF	uterine fibroid

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Table 1

Patient characteristics stratified by index medication

Characteristic	LARC	LA	SARC	TA	Total	*P*jfalue
Participants, *n* (%)	3928 (9.5)	3525 (8.5)	33 000 (79.4)	1108 (2.7)	41 561 (100)	
Age, mean (SD), years	42.2 (6.5)	43.0 (6.2)	42.7 (6.8)	44.0 (5.8)	42.7 (6.7)	<0.001
Region, *n* (%)						<0.001
Midwest	984 (25.1)	914 (25.9)	7739 (23.5)	150 (13.5)	9787 (23.5)	
Northeast	702 (17.9)	879 (24.9)	6290 (19.1)	222 (20.0)	8093 (19.5)	
South	1669 (42.5)	1351 (38.3)	14 139 (42.8)	620 (56.0)	17 779 (42.8)	
West	561 (14.3)	368 (10.4)	4749 (14.4)	115 (10.4)	5793 (13.9)	
Unknown	12 (0.3)	13 (0.4)	83 (0.3)	1 (0.1)	109 (0.3)	
Charlson-Deyo comorbidity index at baseline, *n* (%)						0.006
0	2592 (66.0)	2343 (66.5)	21 736 (65.9)	685 (61.8)	27 356 (65.8)	
1	955 (24.3)	846 (24.0)	8390 (25.4)	311 (28.1)	10 502 (25.3)	
≥2	381 (9.7)	336 (9.5)	2874 (8.7)	112 (10.1)	3703 (8.9)	

ED, emergency department; LA, leuprolide acetate; LARC, long-acting reversible contraceptive steroid; SARC, short-acting reversible contraceptive steroid; TA, tranexamic acid; UF, uterine fibroid.

[a]Values are presented as number and percentage of women unless stated otherwise.

Table 2

Multinomial logistic regression-patient characteristics associated with index medication for the 41 561 study women (SARC is the reference category)

	Index medication[a]		
Predictor	**LARC**	**LA**	**TA**
Age, years			
18–40	Ref	Ref	Ref
41–46	1.10[b] (1.02–1.19)	1.16[c] (1.06–1.27)	1.58[d] (1.35–1.85)
>46	0.83[d] (0.76–0.91)	1.06 (0.97–1.16)	1.50[d] (1.28–1.77)
US Region			
Midwest	Ref	Ref	Ref
Northeast	0.88[b] (0.79–0.97)	1.00 (0.90–1.12)	1.68[d] (1.35–2.09)
South	0.87[c] (0.80–0.95)	0.71[d] (0.64–0.77)	2.01[d] (1.67–2.42)
Unknown	1.18 (0.64–2.17)	1.29 (0.70–2.39)	0.55 (0.08–4.01)
West	0.97 (0.86–1.08)	0.72[d] (0.63–0.82)	1.16 (0.90–1.49)
Comorbidities			
Anaemia	1.26[d] (1.17–1.35)	2.27[d] (2.10–2.44)	1.84[d] (1.62–2.09)
Inflammatory disease	0.86 (0.70–1.06)	1.49[d] (1.25–1.78)	0.61 (0.37–1.00)
Noninflammatory disease	0.88[c] (0.82–0.95)	0.71[d] (0.66–0.78)	0.88 (0.76–1.01)
Endometriosis	1.10 (0.93–1.30)	2.27[d] (1.97–2.61)	0.98 (0.69–1.39)
Benign neoplasm of uterus/ovary	0.90 (0.80–1.02)	0.62[d] (0.53–0.72)	0.49[d] (0.36–0.67)
Pregnancy/delivery	1.64[d] (1.34–2.01)	0.20[d] (0.12–0.32)	1.11 (0.66–1.88)

ED, emergency department; LA, leuprolide acetate; LARC, long-acting reversible contraceptive steroid; SARC, short-acting reversible contraceptive steroid as reference; TA, tranexamic acid; UF, uterine fibroid; Ref, reference.

[a] Values are presented as relative risk ratio (95% CI).

[b] $P < 0.05$;

[c] $P < 0.01$;

[d] $P < 0.001$.

Table 3

Switch patterns stratified for index medication

	Index medication				
Pattern	**LARC (*n* = 3928)**	**LA (*n* = 3525)**	**SARC (*n* = 33 000)**	**TA (*n* = 1108)**	**Total (*n* = 41 561)**
Medication use at follow-up					
Continued index medication, *n* (%)	1,451 (36.9)	14 (0.4)	4,207 (12.7)	43 (3.9)	5,715 (13.8)
Discontinued index medication, *n* (%)	849 (21.6)	1,125 (31.9)	16,656 (50.5)	622 (56.1)	19,252 (46.3)
Switched from index medication, *n* (%)	1,628 (41.4)	2,386 (67.7)	12,137 (36.8)	443 (40.0)	16,594 (39.9)
Second-line treatment among women who switched medication					
Endometrial ablation, *n* (%)	258 (15.8)	505 (21.2)	3160 (26.0)	77 (17.4)	4000 (24.1)
MRgFUS, *n* (%)	0 (0.0)	0 (0.0)	3 (0.02)	0 (0.0)	3 (0.02)
Myomectomy, *n* (%)	63 (3.9)	333 (14.0)	998 (8.2)	22 (5.0)	1416 (8.5)
Uterine artery embolization, *n* (%)	54 (3.3)	27 (1.1)	431 (3.6)	26 (5.9)	538 (3.2)
Hysterectomy, *n* (%)	630 (38.7)	1209 (50.7)	5573 (45.9)	169 (38.1)	7581 (45.7)
Nonindex medication, *n* (%)	623 (38.3)	312 (13.1)	1972 (16.2)	149 (33.6)	3056 (18.4)
Duration of index medication, mean (SD) year	1.3 (1.5)	0.3 (0.4)	0.9 (1.3)	0.4 (0.5)	0.9 (1.3)
Follow-up, mean (SD) year	2.9 (2.2)	3.3 (2.6)	3.1 (2.5)	1.7 (0.9)	3.1 (2.4)

LA, leuprolide acetate; LARC, long-acting reversible contraceptive steroid; MRgFUS, magnetic resonance-guided focused ultrasonography; SARC, short-acting reversible contraceptive steroid; TA, tranexamic acid.

Table 4

Multinomial logistic regression—patient characteristics associated with whether the 41 561 women switched from or discontinued their index medication therapy

Predictor	Discontinued medication RRR (95% CI)	Switched to other therapies RRR (95% CI)
Index medication		
LARC	0.14[a] (0.13–0.15)	0.36[a] (0.33–0.39)
LA	19.23[a] (11.32–32.64)	48.64[a] (28.69–82.46)
SARC	Ref	Ref
TA	4.64[a] (3.39–6.34)	4.29[a] (3.12–5.89)
Age, years		
18–40	Ref	Ref
41–46	1.11[b] (1.03–1.20)	1.30[a] (1.21–1.41)
>46	1.76[a] (1.62–1.91)	1.46[a] (1.34–1.58)
Comorbidity		
Anaemia	1.24[a] (1.15–1.34)	1.79[a] (1.65–1.93)
Inflammatory disease	1.43[a] (1.17–1.74)	1.29[c] (1.05–1.58)
Noninflammatory disease	1.09[c] (1.02–1.17)	0.86[a] (0.80–0.92)
Endometriosis	1.01 (0.87–1.18)	0.89 (0.76–1.04)
Benign neoplasm of uterus/ovary	1.00 (0.90–1.11)	0.67[a] (0.60–0.75)
Pregnancy/delivery	1.17 (0.94–1.44)	0.52[a] (0.41–0.66)
Enrollment time, years	1.37[a] (1.35–1.40)	1.39[a] (1.37–1.42)

ED, emergency department; LA, leuprolide acetate; LARC, long-acting reversible contraceptive steroid; Ref, reference; RRR, relative risk ratio; SARC, short-acting reversible contraceptive steroid; TA, tranexamic acid; UF, uterine fibroid.

[a] $P < 0.001$;

[b] $P < 0.01$;

[c] $P < 0.05$.