**Association Between Menorrhagia and Risk of Intrauterine Device-Related Uterine Perforation and Device Expulsion: Results from the APEX-IUD Study**

Darios GETAHUN, MD, PhD, MPH, Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA; Department of Health Systems Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA

Michael J. FASSETT, MD, Department of Obstetrics & Gynecology, Kaiser Permanente West Los Angeles Medical Center, Los Angeles, CA; Department of Clinical Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA, USA

Jennifer GATZ, PhD, Regenstrief Institute, Indianapolis, IN

Mary Anne ARMSTRONG, MA, Division of Research, Kaiser Permanente Northern California, Oakland, CA

Jeffrey F. PEIPERT, MD, PhD, Indiana University, Indianapolis, IN

Tina RAINE-BENNETT, MD, MPH, Division of Research, Kaiser Permanente Northern California, Oakland, CA; Department of Health Systems Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA*

Susan D. REED, MD, MPH, MS, Department of Obstetrics and Gynecology, University of Washington, Seattle, WA

Xiaolei ZHOU, PhD, RTI Health Solutions, Research Triangle Park, NC

Juliane SCHOENDORF, MD, Bayer AG, Bayer OY, Espoo, Finland

Debbie POSTLETHWAITE, RNP, MPH, Division of Research, Kaiser Permanente Northern California, Oakland, CA*

---

This is the author's manuscript of the article published in final edited form as:

Getahun, D., Fassett, M. J., Gatz, J., Armstrong, M. A., Peipert, J. F., Raine-Bennett, T., Reed, S. D., Zhou, X., Schoendorf, J., Postlethwaite, D., Shi, J. M., Saltus, C. W., Wang, J., Xie, F., Chiu, V. Y., Merchant, M., Alabaster, A., Ichikawa, L. E., Hunter, S., … Anthony, M. S. (2022). Association Between Menorrhagia and Risk of Intrauterine Device-Related Uterine Perforation and Device Expulsion: Results from the APEX-IUD Study. American Journal of Obstetrics and Gynecology. https://doi.org/10.1016/j.ajog.2022.03.025

Jiaxiao M. SHI, PhD, Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA

Catherine W. SALTUS, MA, MPH, RTI Health Solutions, Waltham, MA

Jinyi WANG, MStat, RTI Health Solutions, Research Triangle Park, NC

Fagen XIE, PhD, Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA

Vicki Y. CHIU, MS, Department of Research & Evaluation, Kaiser Pe manente Southern California, Pasadena, CA

Maqdooda MERCHANT, MSc, MA, Division of Research, Kaiser Permanente Northern California, Oakland, CA

Amy ALABASTER, MPH, MS, Division of Research, Kaiser Permanente Northern California, Oakland, CA

Laura E. ICHIKAWA, MS, Kaiser Permanente Washington Health Research Institute, Seattle, WA

Shannon HUNTER, MS, RTI Health Solutions, Research Triangle Park, NC

Theresa M. IM, MPH, Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA

Harpreet S. TAKHAR, MPH, Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA

Mary E RITCHEY, PhD, FISPE, RTI Health Solutions, Research Triangle Park, NC*

Giulia CHILLEMI, MS, Division of Research, Kaiser Permanente Northern California, Oakland, CA

Federica PISA, MD, MStat, Bayer AG, Berlin, Germany

Alex ASIIMWE, PhD, Bayer AG, Berlin, Germany

Mary S. ANTHONY, PhD, RTI Health Solutions, Research Triangle Park, NC

**When the study was conducted.*

**Conflict of Interest:** Funding for this research was provided by Bayer AG, Berlin, Germany to RTI Health Solutions (RTI-HS), Kaiser Permanente Northern California (KPNC), Kaiser Permanente Southern California (KPSC), Kaiser Permanente Washington (KPWA), and Regenstrief Institute (RI). RTI-HS led the study design and conducted analyses with review and interpretation of results in collaboration with KPNC, KPSC, KPWA, RI, and Bayer AG. The contracts between Bayer AG and each of the other organizations (KPNC, KPSC, KPWA, RI, RTI-HS) include independent publication rights  Bayer AG was provided the opportunity to review the manuscript prior to submission and comments were advisory only. MSA, DG, MJF, JMS, FX, VYC, TMI, HST, MAA, DAP  GAC, MM, MER, XZ, SH, JW, SDR, and LI have no competing interests. AA, FP, and JS are employees of Bayer AG, the marketing authorization holder for 3 IUD brands, among others, that were included in this study.

**Financial support:** This study was supported by Bayer AG.

**Role of the funding source:** Authors affiliated with Bayer had a role in designing the study, interpreting the data, and writing the manuscript.

**Disclaimer:** The opinions expressed are solely the responsibility of the authors and do not necessarily reflect the official views of the funding entity.

**Corresponding Author:** Darios Getahun, MD, PhD, MPH, Department of Research & Evaluation, Kaiser Permanente Southern California, 100 S. Los Robles Avenue, 2nd Floor, Pasadena CA 91101

Email: darios.t.getahun@kp.org; Tel: (626) 564-5658; Fax: (626) 564-3409

**Word count:** 2,837

**Condensation:** Diagnosis of menorrhagia in the 12 months before intrauterine device insertion is associated with high risk for expulsion and slightly increased risk for uterine perforation.

**Short title:** Menorrhagia and IUD expulsion and perforation risks

**AJOG at a Glance:**

**A. Why was this study conducted?**

Many women use levonorgestrel-releasing intrauterine devices (LNG-IUDs) to decrease bleeding. The risk of LNG- and Cu-IUD-related uterine perforation and IUD expulsion in women with a recent diagnosis of menorrhagia has not been investigated. We investigated these outcomes by menorrhagia status in 228,834 US women, most with an LNG-IUD, who were >12 months postpartum or nulliparous at IUD insertion.

**B. What are the key findings?**

Compared with women without menorrhagia, women with menorrhagia had higher incidence rates of IUD expulsion (40.01 vs. 10.92/1,000 person years) and slightly higher rates of uterine perforation (0.98 vs. 0.63/1,000 person-years).

**C. What does this study add to what is already known?**

Recent diagnosis of menorrhagia is associated with increased IUD expulsion risk after adjusting for potential confounding factors.

**Highlights:**

- Risk of IUD expulsion was 3-fold higher among women with recent menorrhagia.
- Risk of uterine perforation was low but 1.5-fold higher with menorrhagia.
- The benefit of treatment of HMB with an LNG-IUD may outweigh risk for expulsion.

## ABSTRACT

**Background:** Intrauterine devices are effective contraception, and one levonorgestrel-releasing device is also indicated for treatment of heavy menstrual bleeding (menorrhagia).

**Objective:** To compare the incidence of intrauterine device expulsion and uterine perforation in women with and without a diagnosis of menorrhagia within the 12 months before device insertion.

**Study Design:** Retrospective cohort study conducted in 3 integrated healthcare systems (Kaiser Permanente Northern California, Southern California, and Washington) and a healthcare information exchange (Regenstrief Institute) in the United States, using electronic health records. Nonpostpartum women aged ≤50 years with intrauterine device (e.g., levonorgestrel or copper) insertions from 2001–2018 without a delivery in the prior 12 months were studied in this analysis. Recent menorrhagia diagnosis (i.e., recorded ≤12 months before insertion) was ascertained from *International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* codes. Study outcomes-—device expulsion and device-related uterine perforation (complete or partial)—were ascertained from electronic medical records and validated in data sources. Cumulative incidence and crude incidence rates with 95% confidence intervals were estimated. Cox proportional hazards models estimated crude and adjusted hazard ratios using propensity score overlap weighting (13-16 variables) and 95% confidence intervals.

**Results:** Among 228,834 nonpostpartum women, mean age was 33.1 years, 44.4% were White, and 31,600 (13.8%) had a recent menorrhagia diagnosis. Most women had a levonorgestrel-releasing device (96.4% of those with and 78.2% of those without a menorrhagia diagnosis). Women with a menorrhagia diagnosis were likely to be older, obese, and have dysmenorrhea or fibroids. Women with vs. without a menorrhagia diagnosis had a higher intrauterine device expulsion rate (40.01 vs. 10.92 per 1,000 person-years), especially evident in the few months after insertion. Women with a menorrhagia diagnosis had higher cumulative incidence (95% confidence interval) of expulsion (7.00% [6.70%, 7.32%] at 1 year, 12.03% [11.52%, 12.55%] at 5 years) vs. without (1.77% [1.70%, 1.84%] at 1 year, 3.69% [3.56%, 3.83%] at 5 years). Risk of expulsion was increased for women with a menorrhagia diagnosis vs. without (adjusted hazard ratio, 2.84 [95% confidence interval: 2.66, 3.03]). Perforation rate was low overall (<1/1,000 person-years) but higher in women with a diagnosis of menorrhagia vs without (0.98 vs. 0.63 per 1,000 person-years). Cumulative incidence (95% confidence interval) of uterine perforation was slightly higher for women with a menorrhagia diagnosis (0.09% [0.06%, 0.14%] at 1 year, 0.39% [0.29%, 0.53%] at 5 years) vs. without (0 07% [0.06%, 0.08%], at 1 year, 0.28% [0.24%, 0.33%] at 5 years). Risk of perforation was slightly increased in women with a menorrhagia diagnosis vs. without (adjusted hazard r tio, 1.53; 95% confidence interval, 1.10, 2.13).

**Conclusion:** The risk of expulsion is significantly higher in women with a recent diagnosis of menorrhagia. Patient education and counseling regarding potential expulsion risk is recommended at insertion. The absolute risk of perforation for women with a recent diagnosis of menorrhagia is very low. Increased expulsion and perforation rates observed are likely due to causal factors of menorrhagia.

**Key Words**: intrauterine device, IUD, IUD expulsion, uterine perforation, menorrhagia, heavy menstrual bleeding, electronic health records, natural language processing, algorithm, data linkage, free text, propensity score overlap weighting

## INTRODUCTION

Abnormally heavy or prolonged menstrual bleeding in women of reproductive age, or menorrhagia, affects 10%-30% of women.[1] Heavy menstrual bleeding (HMB) continues to be the foremost cause of hysterectomy, accounting for approximately 45% of all hysterectomy procedures in the United States (US).[2] HMB has long been considered to affect social and emotional well-being, as well as quality of life.[3] It has been suggested that HMB may be an effect of morphological and hemodynamic changes of the uterus, as well as heightened uterine contractility.[4,5] HMB has been associated with uterine fibroids, adenomyosis, endometrial polyps, and coagulopathy.[6-8]

In addition to being a highly effective long-acting reversible contraceptive method, levonorgestrel-releasing intrauterine devices (LNG-IUDs) (20 μg LNG/day) are an effective and US Food and Drug Administration (FDA) approved treatment for HMB.[9] It has been suggested that women with HMB are at inc eased risk for IUD expulsion, with potential mechanisms including brisk bleeding and clotting.[10] Furthermore, it is unknown whether the morphological changes that occur with HMB, along with underlying uterine pathology, may predispose women to potential uterine perforation during IUD use. Therefore, given the relatively high prevalence of HMB among women of childbearing age and the common use of LNG-releasing IUDs for HMB, further investigation is warranted to assess the risks of IUD expulsion and uterine perforation associated with HMB to inform appropriate counseling.

To better understand outcomes associated with IUD use as reflected in US clinical practice, we conducted the APEX-IUD (Association of uterine Perforation and EXpulsion of IUD) study, a multisite retrospective US cohort study of more than 325,000 women to evaluate the incidence and risk factors associated with IUD expulsion and uterine perforation as observed in real-world treatment settings.[11] The objective of the analysis reported here was to estimate the crude incidence rate, cumulative incidence, and risk of IUD expulsion and uterine perforation among women with a diagnosis of menorrhagia in the 12 months before IUD insertion compared with women without such a diagnosis in this time frame.

## MATERIALS AND METHODS

Data for APEX-IUD were obtained from electronic health records (EHRs) within 3 integrated healthcare systems—Kaiser Permanente Northern California (KPNC), Kaiser Permanente Southern California (KPSC), and Kaiser Permanente Washington (KPWA)—and a healthcare information exchange in Indiana, Regenstrief Institute (RI). Study methods for APEX-IUD and validation of the IUD expulsion and uterine perforation outcomes have been previously described in detail.[11,12] All participating research sites received approval or exemption for the conduct of this study by their respective institutional review boards. KPSC also received approval from California Hea th and Human Services Agency and California Department of Public Health Center for Health Statistics and Informatics (i.e., state birth and death files).

### Study Population

The full APEX-IUD population included 326,658 women aged ≤50 years with evidence of an IUD insertion[11] from 2001–2018 who had EHR data available for analysis for a minimum of 12 months prior to IUD insertion. If a woman had more than one IUD insertion during this time period, only the first insertion was used. Only women without evidence of a delivery in the 12 months preceding IUD insertion (n=228,834) were included in the analysis (Figure 1). Women who were less than 12 months postpartum were excluded because menorrhagia is less likely to occur in women who have recently given birth and are breastfeeding.

The first year for inclusion in the study varied by research study site (2001 at RI, 2007 at KPWA, 2009 at KPSC, and 2010 at KPNC), and the last date for inclusion at all sites was April 30, 2018. The date of IUD insertion is referred to as the index date. Women were followed from index date to the earliest outcome date (device expulsion or uterine perforation) or the first of the following censoring events: IUD expulsion (if perforation outcome), removal, reinsertion, or expiration; uterine perforation (if expulsion outcome); pregnancy, hysterec omy or other sterilization procedure; disenrollment from the healthcare system (KP sites); last clinical encounter (RI); end of the study period (June 30, 2018); or death.

**Exposure and Covariates**

Variables for this study were ascertained from EHR systems or a health information exchange utilizing a mixture of structured data (National Drug Codes, *International Classification of Diseases, Ninth Revision/Tenth Revision, Clinical Modification* [ICD-9-CM/10-CM], Healthcare Common Procedure Coding System [HCPCS] and Current Procedural Terminology [CPT] codes) and unstructured data (clinical notes via natural language processing). Operational definitions were initially developed centrally for all study variables and then tailored to each site using combinations of structured and unstructured data.[11] The primary exposure of interest, menorrhagia, was identified via ICD codes (626.2, 626.3, 627.0, N92.0, N92.2, or N92.4) within 12 months before the date of IUD insertion.

Covariates for this analysis included demographics (age, race, and ethnicity) and risk factors at the time of IUD insertion based on all available information during the look-back period, which extended to the earliest enrollment date (KP sites) or clinical encounter (RI) for each woman (12 months minimum). Potential risk factors included smoking status during the past 12 months, body mass index (BMI, kg/m$^2$), parity, gynecologic factors (e.g., diagnosis of dysmenorrhea using ICD codes, diagnosis of uterine fibroids using either or both ICD and CPT codes), cesarean delivery (for women with a delivery before the index date), and indicators of a difficult IUD insertion (e.g., dilation, ultrasound guidance, paracervical block, provider noted difficult insertion, or use of misoprostol), year of index insertion, and IUD type (LNG-IUD or Cu-IUD).[11]

**Outcomes**

The outcomes of interest were any IUD expulsion and any uterine perforation. IUD expulsion was either complete (i.e., IUD located in the vagina, not present in the uterus or abdomen on imaging, or patient reported that the IUD fell out) or partial (i.e., any portion of IUD in the cervix on imaging, documented IUD visualization by a clinician at the cervical os, or IUD malpositioned on imaging and removed by the clinician). Uterine perforation was either complete (i.e., clinical evidence of IUD in the pelvis, abdominal cavity, or adjacent organs) or partial (i.e., IUD removed after being visualized as partially embedded in the myometrium on imaging or hysteroscopy, or partial perforation noted by clinician at the time of removal). Algorithms to identify these outcomes were previously validated in the data sources; during development of the algorithms, a sample of up to one third with a maximum of 100 possible cases of uterine perforation and possible cases of IUD expulsion identified by the algorithm underwent medical record review to determine case status.[12]

**Statistical Analysis**

Descriptive analyses for all variables of interest are presented overall and by menorrhagia status. For categorical variables, frequencies and percentages were calculated for each level. For continuous variables, mean, standard deviation, minimum, maximum, median, and quartiles were examined. Missing data were treated as missing, and no imputations were performed. Where appropriate, variables included a "missing" category for analyses.

Crude incidence rates were calculated as the number of IUD expulsions and uterine perforations divided by the total person-time at risk (in person-years) and were reported as point estimates (number of cases per 1,000 person-years) and 95% confidence intervals (CIs). Crude cumulative incidence, defined as the number of women with IUD expulsions and uterine perforations occurring up to a timepoint out of the number of IUD insertions, was estimated using the Kaplan-Meier method.

Cox regression models were used to estimate crude hazard ratios (HRs) and are reported as point estimates with 95% CIs The proportional hazards assumption between each exposure and outcome pairing was assessed. Adjusted HRs were estimated using a Cox model with propensity score overlap weighting.[13] Propensity score models were developed separately for IUD expulsion and uterine perforation and correspondingly separate weighting was applied for IUD expulsion and uterine perforation. The standardized differences before and after overlap weighting were calculated to evaluate balance in the exposure groups; groups were considered balanced if the standardized difference was less than 0.20 (generally considered small).[14,15] Details for the propensity score models and the overlap weights have been described previously and are presented in Supplemental Appendix A.[11] The following variables were included in the final propensity score models: IUD type, age (continuous for perforation, tertiles for expulsion), race/ethnicity, recent smoker (only for perforation), duration of look-back period (quartiles, only for perforation), calendar year of index date, BMI (categorical), dysmenorrhea, uterine fibroids, parity (0, > 0, or missing), any cesarean delivery (only for perforation), cesarean delivery for the most recent delivery, live birth for the most recent delivery, concomitant gynecologic procedure, indicator of difficult IUD insertion, provider experience (quartiles of number of procedures in most recent calendar year), research site, and age (continuous for perforation and tertile for expulsion) × site interaction. Balance between the 2 exposure groups among the weighted population of women who had no delivery in the previous 12 months was assessed and confirmed. All standardized differences were less than 0.2 after weighting.

All analyses were performed using SAS software, version 9.3 or higher (SAS Institute, Inc., Cary, North Carolina).

## RESULTS

### Cohort Characteristics

Of 228,834 nonpostpartum women, 31,600 (13.8%) women had a recent diagnosis of menorrhagia, and 197,234 women had no such recent history of diagnosis. Among women without a recent diagnosis of menorrhagia, 10,135 (5.1%) had a diagnosis of menorrhagia more than 12 months prior to IUD insertion. Among women with a recent diagnosis of menorrhagia, 96.4% had an LNG-releasing IUD and 2.3% had a Cu-IUD; among women without a recent diagnosis, 78.2% had an LNG-releasing IUD and 20.5% had a Cu-IUD. In both groups, 1.3% of women had an IUD of unknown type.

Women with a recent diagnosis of menorrhagia were more likely than women without a recent diagnosis to have had a prior cesarean delivery (19.1% vs. 11.0%), dysmenorrhea (4.7% vs. 1.2%), and uterine fibroids (24.4% vs. 3.1%) (Table 1). They were also more likely than women without a recent diagnosis to be aged 37 to 50 years (74.9% vs. 33.3%) and obese (48.0% vs. 29.7%) and were less likely to be nulliparous (14.9% vs. 29.0%).

**IUD Expulsion**

The respective crude incidence rate for IUD expulsion among women with and without a recent diagnosis of menorrhagia was 40.01 (95% CI: 38.46, 41.61) and 10.92 (95% CI: 10.59, 11.25) per 1,000 person-years (Table 2). The respective cumulative incidence of IUD expulsion among women with and without a recent menorrhagia diagnosis at 1 year was 7.00% (95% CI: 6.70%, 7.32%) and 1.77% (95% CI: 1.71%, 1.84%) and at 5 years was 12.03% (95% CI: 11.52%, 12.55%) and 3.69% (95% CI: 3.56%, 3.83%) (Figure 2A).

Women with a recent diagnosis of menorrhagia were at higher risk for IUD expulsion than women without a recent diagnosis (crude HR, 3.71; 95% CI: 3.53, 3.90) (Figure 2B). This risk remained but was attenuated after adjustment with propensity score overlap weighting (HR, 2.84; 95% CI: 2.66, 3.03).

**Uterine Perforation**

The crude incidence rate and 5-year cumulative incidence of uterine perforation was very low for both women with and women without a diagnosis of menorrhagia (<1.0 per 1,000 person-years and <0.4%, respectively, in both groups). Among women with and without a recent diagnosis of menorrhagia, the crude incidence rate per 1,000 person-years was 0.98 (95% CI: 0.75, 1.26) and 0.63 (95% CI: 0.56, 0.72), respectively (Table 2). The cumulative incidence of uterine perforation among women with and without a recent diagnosis of menorrhagia, respectively, at 1 year was 0.09% (95% CI: 0.06%, 0.14%) and 0.07% (95% CI: 0.06%, 0.08%), and at 5 years was 0.39% (95% CI: 0.29%, 0.53%) and 0.28% (95% CI: 0.24%, 0.33%) (Figure 3A).

Women with a recent diagnosis of menorrhagia were at slightly higher risk for uterine perforation than women without a recent diagnosis (crude HR, 1.54; 95% CI: 1.16, 2.04) (Figure 3B). This risk remained after propensity score overlap weighting (adjusted HR, 1.53; 95% CI: 1.10, 2.13).

## DISCUSSION

This study showed that, among women without a delivery in the previous 12 months or who were nulliparous, those with a recent diagnosis of menorrhagia were at a threefold increased risk for IUD expulsion, after accounting for various potential confounding factors. Specifically, expulsion crude incidence rate and 1- and 5-year cumulative incidence were considerably higher for women with a diagnosis of menorrhagia in the previous 12 months than in those without. In addition, crude incidence rate and cumulative incidence estimates of uterine perforation, while very low in the entire population (crude incidence rate less than 1 per 1,000 person-years of observation), perforation incidence rates were slightly higher in the women with a recent diagnosis of menorrhagia than in those without. Risk of uterine perforation was approximately 1.5-fold greater in women with a recent diagnosis of menorrhagia than in those without.

Our findings are consistent with prior studies, which observed an increased rate of IUD expulsion among women with HMB.[5,10,16] The association of HMB with IUD expulsion may be related to the mechanisms of brisk bleeding, uterine contractility, and clotting. Alternatively, IUD expulsion may potentially be an effect of inflammatory changes or uterine enlargement or distortion (e.g., caused by uterine fibroids or adenomyosis).[5,10]

To our knowledge, no previous studies have reported the risk of uterine perforation among women with menorrhagia versus those without. We hypothesize that the slightly increased rate of uterine perforation among women with a recent diagnosis of menorrhagia may be attributable to differences in uterine pathology or morphology. Specifically, risks may be related to conditions that potentially compromise the integrity of the uterine wall (e.g., adenomyosis, uterine fibroids, cesarean section scars) and to increased prostaglandin production stimulating contractions that could embed the tip of the IUD.

**Clinical Implications**

Although the risk of expulsion is significantly higher in women with a recent diagnosis of menorrhagia, the potential benefit of treatment of HMB with an LNG-IUD may outweigh this risk for most women. Women with HMB should be aware that they are likely to be at an increased risk of IUD expulsion. At the time of insertion, clinicians should counsel women on the signs and symptoms of IUD expulsion and the potential consequences, including unintended pregnancy if unrecognized. Women with HMB may benefit from more intensive follow-up and surveillance during IUD use. Risks of IUD expulsion and perforation must be balanced with the individual benefits of IUDs as highly effective reversible contraception, and in the case of the LNG-releasing IUD, effective treatment of HMB.

**Research Implications**

Future research could examine additional predictors of IUD expulsion or IUD-related uterine perforation, such as the presence of adenomyosis and uterine fibroids and whether ultrasound use at insertion or more careful follow-up might mitigate these risks. Furthermore, whether the observed associations differ based on the timing of insertion during the menstrual cycle and the severity of menorrhagia warrants further investigation.

**Strengths and Limitations**

A key strength of this study is its large size and sociodemographically diverse cohort of women from different regions of the US with access to healthcare and a high retention rate across the study sites (median: 8.1 years), allowing for a long duration of available data after index date (median: 2.3 years). All outcome measures were previously validated.[12] In addition, the databases used in this study contain detailed covariates from clinical and health claims records that allowed robust propensity score development

Limitations are acknowledged. We were unable to assess the impact of the IUD type (LNG vs. copper) on risk of expulsion and perforation outcomes due to confounding by indication and limited numbers of women with copper IUDs. Surveillance bias can occur when women with and without menorrhagia differ in measurement (i.e., intensity and diagnostic process) or unequal ascertainment of study outcomes during the follow-up period. Also, women with conditions such as adenomyosis and uterine fibroids are likely to have higher surveillance, which might result in greater likelihood of detection of uterine perforation or expulsion. Although the impact of surveillance bias on the results was not formally assessed, we minimized surveillance bias by identifying and including all clinically diagnosed and validated uterine perforation cases and expulsions.[11,12] Use of diagnostic codes to identify dysmenorrhea and diagnostic and procedural codes to identify uterine fibroids may have resulted in incomplete ascertainment, although the use of diagnostic and procedural codes to identify uterine fibroids has previously been validated.[17] Moreover, identification of uterine fibroids did not account for fibroid size or location, which can be challenging to measure and which may have a role in risk of expulsion. Although the analyses were adjusted for many potential confounders through propensity score weighting, the potential for residual confounding due to unmeasured factors remains. Nonetheless, the rate and risk estimates presented are real-world estimates. Data on smoking were self-reported and have not been validated; however, a previous study showed significant agreement between self-reported smoking and serum nicotine metabolite level.[18] Menorrhagia is generally a patient-reported condition in routine clinical practice  and the study did not validate menorrhagia diagnoses. We did not analyze whether perforations and expulsions were partial or complete. While more severe cases of HMB were likely captured with menorrhagia diagnoses, there may have been undocumented cases of HMB. Furthermore, the analyses were adjusted for some conditions potentially associated with HMB (e.g., uterine fibroids), but some associated conditions were not captured (e.g., adenomyosis). Of note, the potential for such undocumented conditions relating to HMB may partially have had a role in the slightly increased risk of uterine perforation in women with a recent diagnosis of menorrhagia.

## CONCLUSION

Women with a recent diagnosis of menorrhagia at IUD insertion were 3-fold more likely to experience IUD expulsion compared with those without a recent diagnosis after adjusting for multiple potential confounding factors, including uterine fibroids and dysmenorrhea. Risk of uterine perforation was low overall but was increased 1.5-fold in women with a recent diagnosis of menorrhagia. Information about the magnitude of risks of IUD expulsion and uterine perforation associated with a history of menorrhagia can help inform counseling and insertion technique, as well as surveillance and intervention strategies.


## ACKNOWLEDGEMENTS

The APEX-IUD study team would like to thank Kaiser Permanente Northern California, Southern California, and Washington members as well as patients represented in the Indiana Health Information Exchange who contributed electronic health information to this study. They would also like to thank Kate Lothman (RTI-HS) for her medical writing contributions.

## REFERENCES


1. Fraser IS, Mansour D, Breymann C, Hoffman C, Mezzacasa A, Petraglia F. Prevalence of heavy menstrual bleeding and experiences of affected women in a European patient survey. Int J Gynaecol Obstet. 2015 Mar;128(3):196-200.

2. Cohen SL, Vitonis AF, Einarsson JI. Updated hysterectomy surveillance and factors associated with minimally invasive hysterectomy. JSLS. 2014 Jul-Sep;18(3):e2014.00096.

3. Karlsson TS, Marions LB, Edlund MG. Heavy menstrual bleeding significantly affects quality of life. Acta Obstet Gynecol Scand. 2014 Jan;93(1):52-7.

4. Ting SO, Burke C. Ultrasound assessment of uterine morphology in menorrhagia: case control study. J Obstet Gynaecol. 2020 Feb;40(2):260-263. doi: 10.1080/01443615.2019 1622084. Epub 2019 Jul 29. PMID: 31352859.

5. Youm J, Lee HJ, Kim SK, Kim H, Jee BC. Factors affecting the spontaneous expulsion of the levonorgestrel-releasing intrauterine system. Int J Gynaecol Obstet. 2014 Aug;126(2):165-9.

6. Singh S, Best C, Dunn S, Leyland N, Wolfman WL; Clinical Practice – Gynaecology Committee. Abnormal uterine bleeding in pre-menopausal women. J Obstet Gynaecol Can. 2013 May;35(5):473-475.

7. Hapangama DK, Bulmer JN. Pathophysiology of heavy menstrual bleeding. Womens Health (Lond). 2016 Jan;12(1):3-13.

8. Tower AM, Frishman GN. Cesarean scar defects: an underrecognized cause of abnormal uterine bleeding and other gynecologic complications. J Minim Invasive Gynecol. 2013 Sep-Oct;20(5):562-72.

9. Bayer HealthCare Pharmaceuticals Inc. Mirena (levonorgestrel-releasing intrauterine system) [prescribing information]. August 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021225Orig1s040lbl.pdf. Accessed April 1, 2021.

10. Kaunitz AM, Inki P. The levonorgestrel-releasing intrauterine system in heavy menstrual bleeding: a benefit-risk review. Drugs. 2012 Jan 22;72(2):193-215.

11. Anthony MS, Reed SD, Armstrong MA  Getahun D, Gatz JL, Saltus CW, et al. Design of the Association of Uterine Perforation and Expulsion of IUD (APEX-IUD) study: a multisite retrospective cohort study. Am J Obstetrics Gynecol. 2021. Epub ahead of print.

12. Anthony MS, Armstrong MA, Getahun D, Scholes D, Gatz J, Schulze-Rath R, et al. Identification and validation of uterine perforation, intrauterine device expulsion, and breastfeeding in four health care systems with electronic health records. Clin Epidemiol. 2019;11:635-43.

13. Li F, Morgan KL, Zaslavsky AM. Balancing covariates via propensity score weighting. J Am Stat Assoc. 2018 2018/01/02;113(521):390-400.

14. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015 Dec 10;34(28):3661-79.

15. McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. Stat Med. 2013 Aug 30;32(19):3388-414.

16. Madden T, McNicholas C, Zhao Q, Secura GM, Eisenberg DL, Peipert JF. Association of age and parity with intrauterine device expulsion. Obstet Gynecol. 2014 Oct;124(4):718-26.

17. Yu O, Reed SD, Schulze-Rath R, Grafton J, Hansen K, Scholes D. Identification of incident uterine fibroids using electronic medical record data. EGEMS (Wash DC). 2019;7(1):5.

18. Buka SL, Shenassa ED, Niaura R. Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: a 30-year prospective study. Am J Psychiatry 2003;160(11):1978–1984

**Table 1. Characteristics of study cohort at or before index date, based on menorrhagia diagnosis status within 12 months before IUD insertion**

| | Recent menorrhagia diagnosis | | Unweighted absolute standardized differences[a] |
|---|---|---|---|
| **Characteristic** | **Yes (N = 31,600)** | **No (N = 197,234)** | |
| Person-years at risk | 62,405.4 | 390,598.3 | |
| Age, mean (SD), y | 40.1 (7.64) | 32.0 (8.62) | 0.987 |
| Age category, n (%), y | | | |
| ≤28 | 2,832 (9.0) | 74,660 (37.9) | 0.726 |
| 29-36 | 5,112 (16.2) | 56,956 (28.9) | 0.308 |
| 37-50 | 23,656 (74.9) | 65,618 33.3) | 0.918 |
| Race/ethnicity, n (%) | | | |
| Asian/Pacific Islander | 3,060 (9.7) | 23 284 (11.8) | 0.069 |
| Hispanic Black | 89 (0.3) | 392 (0.2) | 0.017 |
| Hispanic Other | 6,433 (20.4) | 34,312 (17.4) | 0.076 |
| Hispanic White | 4,031 (12.8) | 18,119 (9.2) | 0.114 |
| Non-Hispanic Black | 3,680 (11 6) | 17,047 (8.6) | 0.100 |
| Non-Hispanic White | 12,571 (39 8) | 88,975 (45.1) | 0.108 |
| Other or multiple | 1,293 (4.1) | 10,221 (5.2) | 0.052 |
| Unknown | 443 (1.4) | 4,884 (2.5) | 0.078 |
| Body mass index (kg/m$^2$), n (%) | | | |
| Underweight | 183 (0.6) | 2,940 (1.5) | 0.090 |
| Normal weight | 7,431 (23.5) | 76,860 (39.0) | 0.338 |
| Overweight | 8,618 (27.3) | 54,075 (27.4) | 0.003 |
| Obese | 15,156 (48.0) | 58,577 (29.7) | 0.381 |
| Missing | 212 (0.7) | 4,782 (2.4) | 0.142 |
| Recent smoker, n (%) | 3,349 (10.6) | 21,349 (10.8) | 0.007 |
| Prior history of cesarean, n (%) | 6,031 (19.1) | 21,612 (11.0) | 0.229 |
| Nullipara, n (%) | 4,698 (14.9) | 57,217 (29.0) | 0.347 |
| IUD type, n (%) | | | |
| LNG | 30,455 (96.4) | 154,278 (78.2) | 0.567 |
| Copper | 728 (2.3) | 40,395 (20.5) | 0.597 |
| Unknown | 417 (1.3) | 2,561 (1.3) | 0.002 |

| Characteristic | Recent menorrhagia diagnosis | | Unweighted absolute standardized differences[a] |
|---|---|---|---|
| | Yes (N = 31,600) | No (N = 197,234) | |
| Dysmenorrhea, n (%) | 1,498 (4.7) | 2,340 (1.2) | 0.211 |
| Prior history of fibroids, % | 7,705 (24.4) | 6,031 (3.1) | 0.652 |
| Any difficult insertion, % | 3,699 (11.7) | 23,098 (11.7) | 0.000 |

Abbreviations: IUD, intrauterine device; LNG, levonorgestrel; SD, standard deviation.

Women were >12 months from delivery or nulliparous.

[a] Standardized differences assess the difference between groups.[14] An absolute value of < 0.2 is generally considered as small.[15]

**Table 2. Crude incidence rates and 1-year and 5-year cumulative incidence rates for IUD-related uterine perforation and expulsion based on menorrhagia diagnosis status within 12 months before IUD insertion**

| | Person-years | Number of events | Crude incidence rate (95% CI)[a] | Crude cumulative incidence (95% CI) | |
|---|---|---|---|---|---|
| | | | | 1 Year, % | 5 Years, % |
| **IUD expulsion** | | | | | |
| Menorrhagia | 62,405 | 2,497 | 40.01 (38.46, 41.61) | 7.00 (6.70, 7.32) | 12.03 (11.52, 12.55) |
| No menorrhagia | 390,598 | 4,265 | 10.92 (10.59, 11.25) | 1.77 (1.71, 1.84) | 3.69 (3.56, 3.83) |
| **Uterine perforation** | | | | | |
| Menorrhagia | 62,405 | 61 | 0.98 (0 75, 1.26) | 0.09 (0.06, 0.14) | 0.39 (0.29, 0.53) |
| No menorrhagia | 390,598 | 248 | 0.63 (0.56, 0.72) | 0.07 (0.06, 0.08) | 0.28 (0.24, 0.33) |

Abbreviations: CI, confidence interval; IUD, intrauterin device.

Women were >12 months from delivery or nulliparous.

[a] Per 1,000 person-years.

## FIGURE LEGENDS

**Figure 1. Study Design and Menorrhagia Cohorts**

Abbreviations: IUD, intrauterine device; KPNC, Kaiser Permanente Northern California; KPSC, Kaiser Permanente Southern California; KPWA, Kaiser Permanente Washington; RI, Regenstrief Institute.

**Figure 2A and 2B. A) Cumulative incidence and B) crude and adjusted[a] hazard ratios (log scale) for the association between menorrhagia diagnosis status within 12 months before IUD insertion and IUD expulsion**

**A.**

**B.**

Abbreviations: BMI = body mass index; CI, confidence interval; HR, hazard ratio; IUD, intrauterine device.
Women were >12 months from delivery or nulliparous.

[a] The adjusted HRs (recent menorrhagia vs. not) were calculated using the Cox model weighted with propensity score overlap weights. The following variables were included in the propensity score models for adjustment: IUD type, age (continuous for perforation, tertiles for expulsion), race/ethnicity, recent smoker (only for perforation), duration of look-back period (quartiles, only for perforation), calendar year of index date, BMI (categorical), dysmenorrhea, uterine fibroids, parity (0, >0, or missing), cesarean delivery any time before index date (only f r perforation), cesarean delivery for the most recent delivery, live birth for the most recent delivery, concomitant gynecologic procedure, indicator of difficult IUD insertion, provider experience (quartiles), research site, and age (continuous for p rforation and tertile for expulsion) × site interaction.

**Figure 3A and 3B. A) Cumulative incidence and B) crude and adjusted[a] hazard ratios (log scale) for the association between menorrhagia diagnosis status within 12 months before IUD insertion and IUD-related uterine perforation**

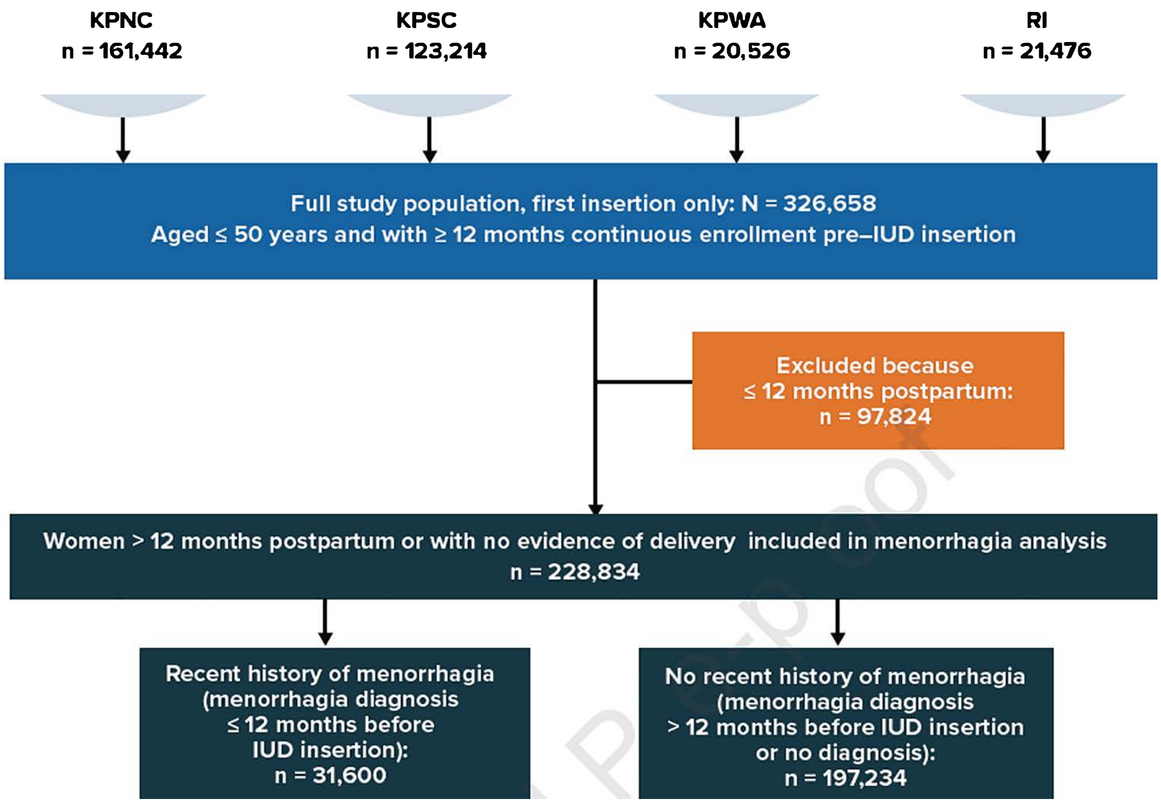
**A.**

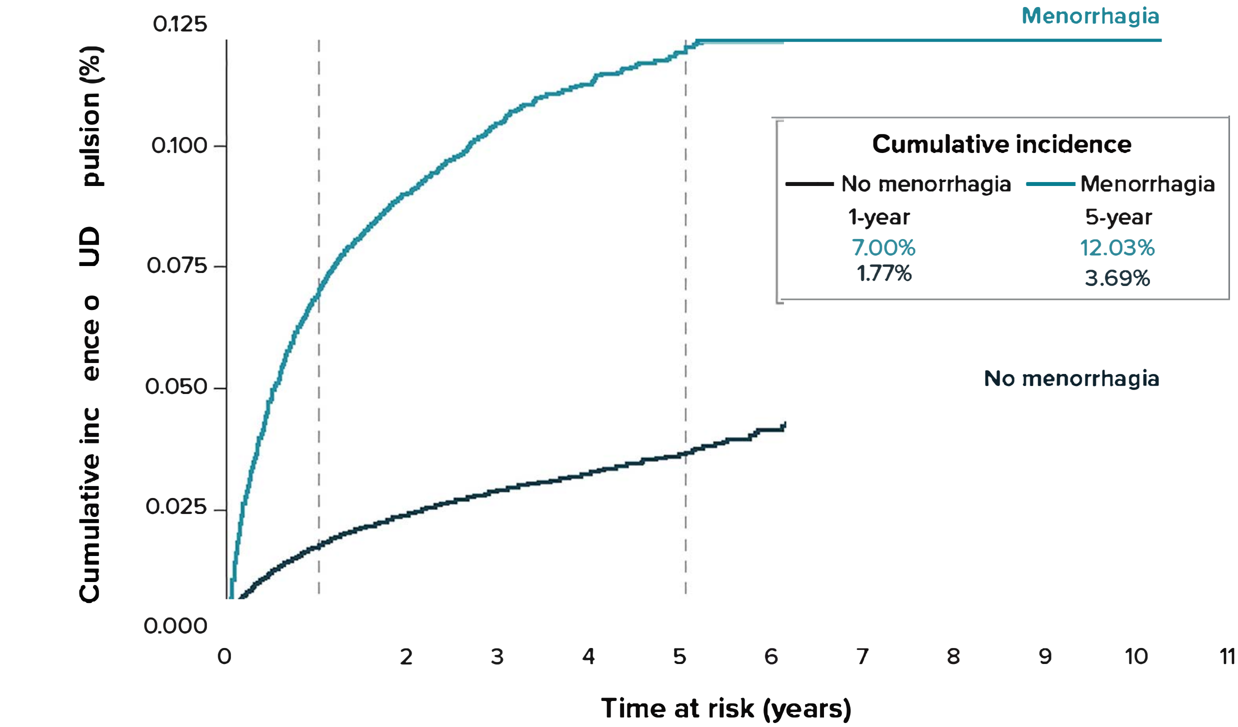
**B.**

Abbreviations: BMI = body mass index; CI, confidence interval; HR, hazard ratio; IUD, intrauterine device.
Women were > 12 months from delivery or nulliparous.

[a] The adjusted HRs (recent menorrhagia vs. not) were calculated using the Cox model weighted with propensity score overlap weights. The following variables were included in the propensity score models for adjustment: IUD type, age (continuous for perforation, tertiles for expulsion), race/ethnicity, recent smoker (only for perforation), duration of look-back period (quartiles, only for perforation), calendar year of index date, BMI (categorical), dysmenorrhea, uterine fibroids, parity (0, >0, or missing), cesarean delivery any time before index date (only for perforation), cesarean delivery for the most recent delivery, live birth for the most recent delivery, concomitant gynecologic procedure, indicator of difficult IUD insertion, provider experience (quartiles), research site, and age (continuous for perforation and tertile for expulsion) × site interaction.

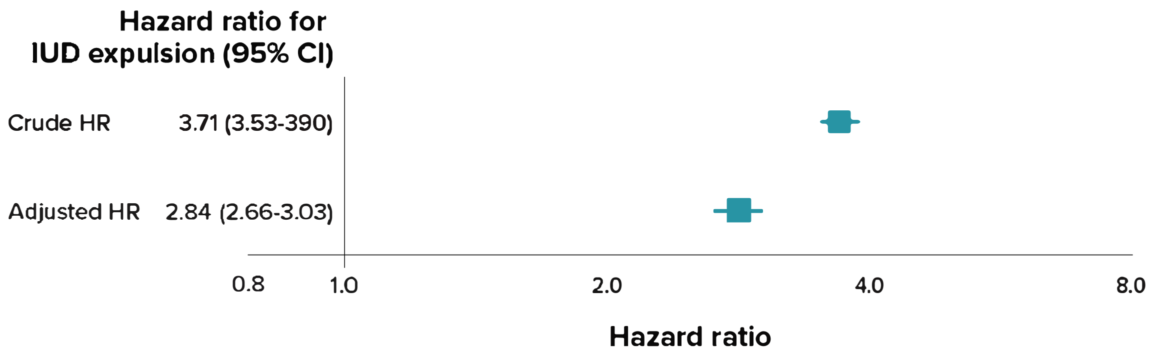
Note: The rapid increase in cumulative incidence shortly after 5 years may have been due to decreasing numbers of patients, resulting in unstable rates.

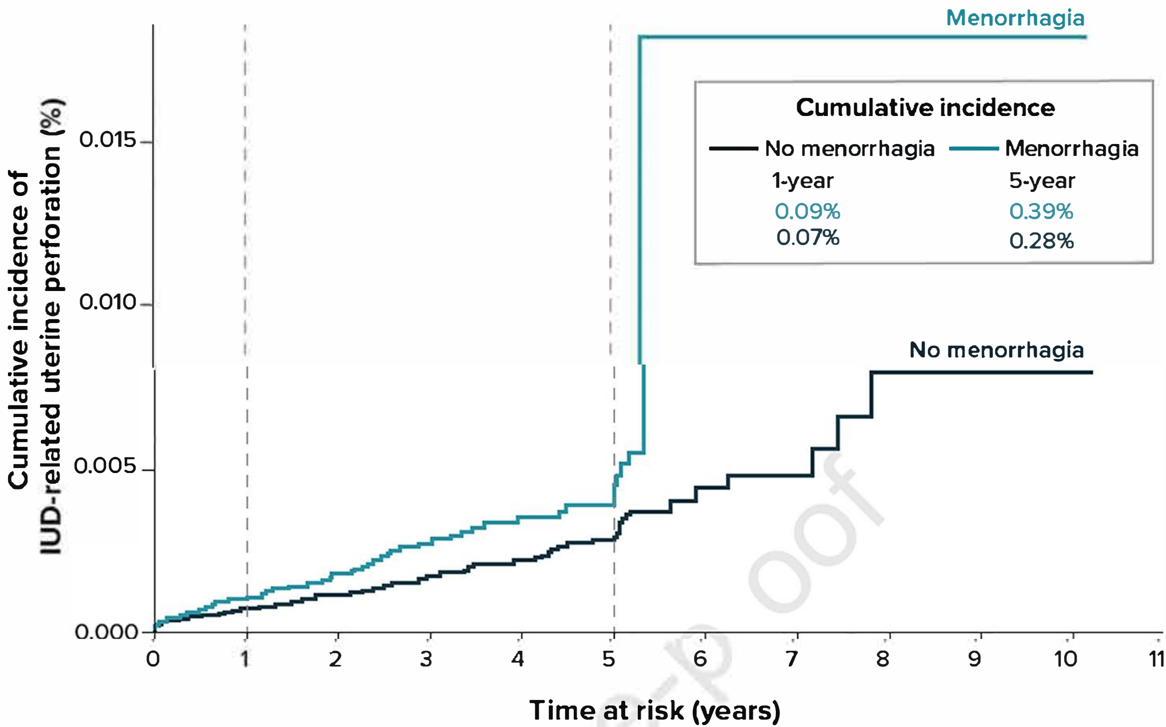

KPNC
n = 161,442
KPSC
n = 123,214
KPWA
n = 20,526
RI
n = 21,476
Full study population, first insertion only: N = 326,658
Aged ≤ 50 years and with ≥ 12 months continuous enrollment pre–IUD insertion
Excluded because
≤ 12 months postpartum:
n = 97,824
Women > 12 months postpartum or with no evidence of delivery included in menorrhagia analysis
n = 228,834
Recent history of menorrhagia
(menorrhagia diagnosis
≤ 12 months before
IUD insertion):
n = 31,600
No recent history of menorrhagia
(menorrhagia diagnosis
> 12 months before IUD insertion
or no diagnosis):
n = 197,234




**Number of patients at risk**

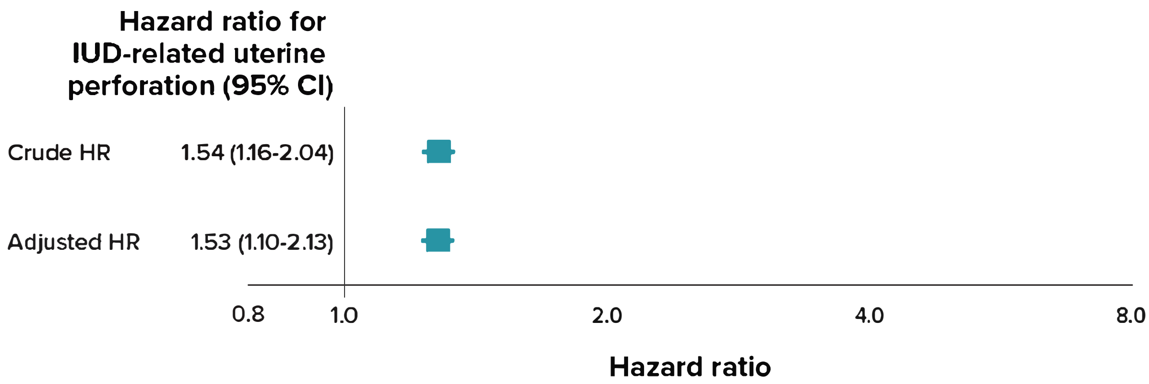
| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No menorrhagia | 197,234 | 119,728 | 76,315 | 50,968 | 33 995 | 18,353 | 2,499 | 1,404 | 597 | 122 | 14 | 0 |
| Menorrhagia | 31,600 | 18,370 | 12,440 | 8,724 | 6,023 | 3,411 | 57 | 33 | 15 | 6 | 2 | 0 |


Hazard ratio for
IUD expulsion (95% CI)
Crude HR
3.71 (3.53-390)
Adjusted HR
2.84 (2.66-3.03)
0.8
1.0
2.0
4.0
8.0
Hazard ratio




**Number of patients at risk**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No menorrhagia | 197,234 | 119,728 | 76,315 | 50,968 | 33 995 | 18,353 | 2,499 | 1,404 | 597 | 122 | 14 | 0 |
| Menorrhagia | 31,600 | 18,370 | 12,440 | 8,724 | 6,023 | 3,411 | 57 | 33 | 15 | 6 | 2 | 0 |



Hazard ratio for IUD-related uterine perforation (95% CI)
Crude HR
1.54 (1.16-2.04)
Adjusted HR
1.53 (1.10-2.13)
0.8
1.0
2.0
4.0
8.0
Hazard ratio