Design of the Association of Uterine Perforation and Expulsion of IUD (APEX-IUD) Study: A Multisite Retrospective Cohort Study

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Condensation: Design and methods of a retrospective, multisite cohort study assessing the association of postpartum timing and breastfeeding with intrauterine device perforation and expulsion are presented.

Short Title: APEX-IUD Study Methods

AJOG at a Glance:

A. Why was the study conducted? EURAS-IUD showed increased risk of uterine perforation among women who were breastfeeding or ≤36 weeks postpartum at intrauterine device (IUD) insertion. FDA suspected differences in breastfeeding

practices and postpartum timing of IUD placement in the US and mandated a study to assess risks among US women.

B. What are the key findings? Retrospective, real-world data can be used to estimate risks with more timely results than are achieved with prospective studies. Pooling data across multiple sites can provide demographic variation and confirm results across sites.

C. What does this study add to what is already known? APEX-IUD study design and patient characteristics are presented. Final study results will provide valuable information for clinical practice based on real-world evidence about risk of perforation and expulsion.

Key words: breastfeeding, electronic health record data, evidence, Food and Drug Administration (FDA), intrauterine, intrauterine device (IUD), IUD expulsion, IUD perforation, natural language processing, menorrhagia

Highlights:

- Multisite retrospective APEX-IUD cohort study methods and cohort data presented
- Study mandated by FDA evaluating IUD-related uterine perforation and IUD expulsion
- Key risk factors: breastfeeding and postpartum timing at IUD insertion
- Variables identified through structured data and natural language processing
- 326,658 women with ≥1 IUD insertion; median continuous enrollment 7.5 years

STRUCTURED ABSTRACT

BACKGROUND: Intrauterine devices (IUDs) are effective and safe, long-acting reversible contraceptives, but risk of uterine perforation occurs with an estimated incidence of 1-2 per 1,000 insertions. EURAS-IUD, a European prospective observational study that enrolled 61,448 participants (2006-2012), found that women breastfeeding at the time of device insertion or with the device inserted ≤36 weeks postpartum had higher risk of uterine perforation. APEX-IUD (Association of uterine Perforation and EXpulsion of IUD) is a Food and Drug Administration–mandated study designed to reflect current United States clinical practice. The aims of APEX-IUD are to evaluate risk of IUD-related uterine perforation and device expulsion among women who are breastfeeding or within 12 months postpartum at insertion.

OBJECTIVE: We describe the APEX-IUD study design, methodology, and analytic plan and present study population characteristics, size of risk-factor groups, and duration of follow-up.

STUDY DESIGN: APEX-IUD is a retrospective cohort study conducted in four organizations with access to electronic health records: Kaiser Permanente Northern California (KPNC), Kaiser Permanente Southern California (KPSC), Kaiser Permanente Washington (KPWA), and Regenstrief Institute (RI) in Indiana. Variables were identified through structured data (e.g., diagnostic, procedural, medication codes) and unstructured data (e.g., clinical notes) via natural language processing. Outcomes include uterine perforation and device expulsion; potential risk factors are breastfeeding at insertion, postpartum timing of insertion, device type, and menorrhagia diagnosis within the year prior to insertion. Covariates include demographic characteristics, clinical characteristics, and procedure-related variables, such as difficult insertion. The first potential date of inclusion for eligible women varies by research site (January

1, 2001-January 1, 2010). Follow-up begins at insertion and ends at first occurrence of an outcome of interest, a censoring event (device removal/reinsertion, pregnancy, hysterectomy, sterilization, device expiration, death, disenrollment, last clinical encounter), or end of study period (June 30, 2018). Comparisons between levels of exposure variables will be made using Cox regression models with confounding adjusted by propensity score weighting using overlap weights.

RESULTS: The study population includes 326,658 women with at least one device insertion during the study period (KPNC: 161,442; KPSC: 123,214; KPWA: 20,526; RI: 21,476). Median duration of continuous enrollment was 90 (74-177) months. Mean age was 32 years, and the population was racially and ethnically diverse across the four sites. Mean body mass index was 28.5 kg/m^2, 10.0% had menorrhagia ≤12 months before insertion, 5.3% had uterine fibroids, and 10% of women were recent smokers; 79.4% had levonorgestrel-releasing devices and 19.5% had copper devices. Across sites, 97,824 women had an insertion ≤52 weeks postpartum, of which 94,817 (97%) had breastfeeding status determined at insertion; 228,834 women had device insertion >52 weeks postpartum or no evidence of a delivery in their health record.

CONCLUSION: Combining retrospective data from multiple sites allowed for a large and diverse study population. Collaboration with clinicians in the study design and validation of outcomes ensured that APEX-IUD results reflect current United States clinical practice. Results from this study will provide valuable information based on real-world evidence about risk factors for IUD perforation and expulsion for clinicians.

INTRODUCTION

Although intrauterine devices (IUDs) are highly effective long-acting reversible contraceptives,[1] their use carries a risk of uterine perforation, with estimated incidences of 1-2 perforations per 1,000 insertions.[1,3] These rates were reported by the prospective observational European Active Surveillance Study for Intrauterine Devices (EURAS-IUD), designed to evaluate the risk of uterine perforation among users of levonorgestrel (LNG)-releasing and copper IUDs used in a routine clinical setting, conducted in six European countries, with recruitment from 2006-2012.[4] Two cohorts were included in this study: new users of LNG-releasing IUDs (n = 43,078) or copper IUDs (n = 18,370), with follow-up after 12 months. The study did not identify a relevant difference in perforation rate by IUD type; however, this study suggested that breastfeeding at the time of IUD insertion was associated with a 6-fold increase in relative risk of uterine perforation. There was also an increased risk of uterine perforation among those with IUD insertions within 36 weeks after the most recent delivery.

Consistent with clinical practice in the European countries participating in the study, EURAS-IUD provided little data on IUD placement immediately postpartum, a more-accepted practice in the United States (US).[1] Given the results of EURAS-IUD,[4] the US Food and Drug Administration (FDA) mandated a study to evaluate uterine perforation risks associated with US clinical practices for IUD insertion. Although FDA initially recommended a prospective observational study, the research team instead suggested that a retrospective study drawing data from electronic health records (EHRs) would provide greater efficiency and more timely results while reflecting current US clinical practice. Following a validation study demonstrating that algorithms could be used to identify uterine perforation and IUD expulsion in proposed data

sources and that breastfeeding could be identified in EHRs of women who had given birth,[5] the APEX-IUD (Association of uterine Perforation and EXpulsion of IUD) study was planned in coordination with Bayer and FDA.

APEX-IUD is a multisite, retrospective cohort study using data from EHRs and a health information exchange assessing the outcomes of uterine perforation and IUD expulsion in association with potential risk factors, including breastfeeding, postpartum timing of IUD insertion, recent history of menorrhagia, and IUD type in the setting of usual healthcare.[6] This manuscript details the study design, methodology, and characteristics of the study population. Comparisons with the methods of the prospective cohort study, EURAS-IUD, are also discussed. The study results of APEX-IUD will be described separately.

MATERIALS AND METHODS

Study Population

The study population included all women aged ≤50 years with evidence of an IUD insertion and with ≥12 months of enrollment history preceding IUD insertion (for Kaiser Permanente [KP] sites) or a clinical visit ≥12 months before insertion (for Regenstrief Institute [RI]). The first potential date for a woman's inclusion in the study varies by research site based in part on when EHR data became available at the beginning of the year at each site, in 2001 at RI, 2007 at Kaiser Permanente (KP) Washington (KPWA), 2009 at KP Southern California (KPSC), and 2010 at KP Northern California (KPNC); and the last date for inclusion at all sites is April 30, 2018. All IUD insertions from eligible women are included.

Study Design

APEX-IUD is a retrospective cohort study. Among women with an IUD insertion identified within EHR data, this study will evaluate the association of two primary potential risk factors, breastfeeding status at the time of IUD insertion and timing of IUD insertion during the postpartum period, and the outcomes of IUD-related uterine perforation and IUD expulsion in the usual healthcare setting (i.e., the data are abstracted from patient care records rather than data collected for a clinical trial). The association of two secondary potential risk factors, recent history of menorrhagia and IUD type, and said outcomes will also be evaluated. Women will be followed from IUD insertion date (index date) until the earliest date of: IUD-related uterine perforation, IUD expulsion, IUD removal, IUD reinsertion, pregnancy, hysterectomy or other sterilization procedure, IUD expiration, disenrollment from the healthcare system (KP sites), last clinical encounter (RI), end of the study period (June 30, 2018), or death. All person-time at risk is included with no requirements for minimum or maximum follow-up time.

All participating research sites received approval or waiver for the conduct of this study by their respective institutional review boards. KPSC also received approval from California Health and Human Services Agency and California Department of Public Health Center for Health Statistics and Informatics (state birth and death files). Each site submitted data for analysis in a de-identified, standard format according to a data structure template for variables in Table 1.

Data Sources

Data are from three integrated healthcare systems with EHRs (KPNC, KPSC, and KPWA) and RI, an organization with research access to a health information exchange with access to EHRs.

These study sites were included based on their ability to access population-based EHR data, data quality, and variation in demographics. Appendix A (supplemental material) provides additional detail.

Potential risk factors, covariates, and outcomes are identified from the EHRs and include both structured data (e.g., ICD-9/10-CM [*International Classification of Diseases, Ninth Revision/Tenth Revision, Clinical Modification*] diagnosis and procedure codes, medication codes, Common Procedural Terminology codes, and Healthcare Common Procedural Coding System codes) and unstructured data (e.g., clinical notes). Algorithms were also developed to identify potential risk factors and outcomes using operational definitions, natural language processing (NLP), and chart review at all sites.[5] These algorithms were developed collaboratively to capture the same concepts, but implemented separately at each site and differed where appropriate; for instance, some ICD codes performed better at some sites than others due to variation in local coding practices. Algorithms for the outcome variables, uterine perforation and IUD expulsion, were validated by obstetrician-gynecologist clinicians from each site via chart review prior to use of ICD-10-CM coding. The proportions of women at risk who had one of these outcomes were calculated and compared before and after the implementation of ICD-10-CM coding to assess temporal consistency over coding terms (see Appendix B, supplemental material).

Potential Risk Factors

Two primary risk factors are evaluated: time of IUD insertion postpartum and breastfeeding status at time of IUD insertion. Postpartum time of IUD insertion, originally categorized into four discrete time periods in agreement with FDA, was later expanded to five, such that the ≤6-

week period (which was strongly bimodal) was further divided: (1) 0 to ≤3 days, (2) >3 days to ≤6 weeks, (3) >6 to ≤14 weeks, (4) >14 to ≤52 weeks, and (5) >52 weeks or with no evidence of delivery. Breastfeeding status at the time of IUD insertion was classified as yes (last breastfeeding date within 30 days before IUD insertion or any time after IUD insertion, up to 52 weeks after delivery), no (last breastfeeding date >30 days before IUD insertion or first non-breastfeeding date before IUD insertion), or undetermined. Women with undetermined breastfeeding status will be excluded from the breastfeeding cohort analyses. Other key potential risk factors include recent menorrhagia, defined as a menorrhagia code in the 12 months before IUD insertion, and IUD type (LNG-IUDs, including 52 mg, 19.5 mg, and 13.5 mg reservoir devices; and copper IUDs).

Outcomes

Two key outcomes are assessed: (1) uterine perforation, defined as complete perforation (with clinical evidence of IUD in the pelvis or abdominal cavity) or partial perforation (i.e., IUD removed after being visualized as partially embedded in the myometrium on imaging or hysteroscopy, or partial perforation noted by clinician at time of removal); and (2) IUD expulsion, defined as complete expulsion (IUD located in the vagina, not present in the uterus or abdomen on imaging, or patient reported IUD fell out) or partial expulsion (any portion of IUD in the cervix on imaging, documented visualization by a clinician, or IUD considered malpositioned on imaging and removed by the clinician). At RI, KPNC, and KPWA, potential uterine perforations identified by structured and unstructured data were confirmed by chart review.

Covariates

Demographic and clinical characteristics are assessed before the index date for each eligible IUD insertion. All available data but a minimum of 12 months before the index date are used to evaluate women's characteristics and potential confounders, thus reducing misclassification of demographic and clinical characteristics.[7] Demographic covariates include age, self-reported race/ethnicity and smoking status, month and year of the index date, and duration of the lookback period; clinical covariates include body mass index (BMI, kg/m^2), dysmenorrhea, uterine fibroids, parity, cesarean delivery (for women with a delivery before the index date), and indicators of a difficult insertion (Table 1). Other procedure-related characteristics (e.g., concomitant gynecologic procedure) and clinician-related covariates (e.g., number of IUD insertions in the previous year) were also collected (Table 1).

Study Variables

For the outcome evaluations, person-time at risk will be calculated from the IUD insertion date until the first occurrence of an outcome or censoring date, at which point follow-up ends for that woman. The censoring date will be the earliest of the following dates: IUD removal or reinsertion, start of new pregnancy, hysterectomy, bilateral oophorectomy and other types of sterilization, expiration of IUD, disenrollment from the healthcare system (KP sites), last clinical encounter in the healthcare system (RI), death, and end of the study period (June 30, 2018).

Study Size

Power calculations for uterine perforation using the expected number of IUD insertions and risk-factor allocation based on the validation study[5] and EURAS-IUD[4] were performed by using PASS 14 software (NCSS, LLC, Kaysville, Utah) for a two-sided test of the hazard ratio (HR)[8].

Because IUD expulsion rates are higher than uterine perforation rates, power for IUD expulsion comparisons is greater than for perforation.

Statistical Analysis

Descriptive analyses for all variables of interest were conducted overall and stratified by research site. For categorical variables, frequencies and percentages were calculated. For continuous variables, the mean, standard deviation, minimum, maximum, median, and quartiles were computed. Missing data were treated as missing and no imputations were performed. All analyses were performed using SAS software, version 9.3 or higher (SAS Institute, Inc., Cary, North Carolina).

Crude incidence rates and cumulative incidence of the outcomes will be estimated for each risk-factor group (e.g., breastfeeding status and postpartum IUD insertion timing). Crude HRs will be calculated for each outcome for each site. Confounding in the multivariable models will be controlled through propensity scores based on the values of covariates at the time of IUD insertion. Separate propensity score models will be developed by using logistic regression for each pairing of a potential risk factor with an outcome. Covariates will be assessed for inclusion in propensity score models based on association with the study outcome if the crude HR is greater than 1.11 or less than 0.90 and not outcome-blinded. Additional confounders will be selected for inclusion if at least a 10% change in the HR of the risk factor–outcome relationship occurs when adjusting for that variable. From the fitted logistic regression models, propensity scores will be estimated for each IUD insertion.

Propensity scores will be used to calculate weights for each IUD insertion within each risk-factor group. The weights will be “overlap weights.”[9] This method has an advantage of not

requiring trimming of observations; rather, observations with significant overlap between groups are up-weighted, and observations with very little overlap are down-weighted, compared with regular inverse probability treatment weighting. To assess whether covariates were balanced across risk-factor groups after weighting, the distribution of each variable was compared between categories of the risk-factor variable, and balance parameters (i.e., standardized differences)[10] will be calculated. Appendix C (supplemental material) provides additional detail.

RESULTS

The results presented include a description of the study design, methodology, and characteristics of the study population. The final study results will be published separately.

Participants

The study includes 326,658 women with at least one IUD insertion identified during the study period. The number of women included from each study site differed (KPNC, 161,442; KPSC, 123,214; KPWA, 20,526; and RI, 21,476). Approximately 19% of women had multiple insertions; the information reported here reflects only the first IUD insertion.

Size of Risk-Factor Groups

Nearly 95,000 women across all sites had an IUD insertion within 52 weeks after delivery and had information in their EHR sufficient to determine breastfeeding status at IUD insertion. Twice as many of these women were determined to be breastfeeding at the time of IUD insertion (n=64,186) than not breastfeeding (n=30,631) (Table 2, Figure 1). Most women in the study (n = 228,834 of 326,658) had an IUD placement more than 52 weeks postpartum or had no evidence of a delivery in their EHR. At the time of the first identified IUD insertion, 10% (range

across sites, 5.6%-12.8%) of women had a menorrhagia diagnosis within 12 months before IUD insertion. Approximately 79% of the first identified IUD insertions were LNG-releasing IUDs; 20% were copper IUDs; and for about 1%, IUD type was not available.

Censoring Events and Duration of Continuous Enrollment

Reasons for censoring were similar across sites and overall (Table 3). Removal and/or replacement of IUD (32.0%), end of study period (32.0%), and end of enrollment/follow-up (25.6%) accounted for the majority (89.6%) of censoring events. The proportion of censoring because of IUD expiration, the approach used if no other censoring event or outcome occurred before this time, was 4.5%. Across all sites, median duration of continuous enrollment was 90.0 (site range, 74.0-176.8) months (Table 4). Median continuous enrollment after the index date was 28.7 (site range, 21.8-30.7) months overall.

Baseline Characteristics

Table 5 provides demographics and characteristics of the study population stratified by research site. The average age in this population was 32 years, and the population was racially and ethnically diverse across the four sites. Mean BMI was 28.5 kg/m^2 (standard deviation, 7.0 kg/m^2); 10% of women were recent smokers. Population characteristics were generally well-balanced across sites, with some variation by site in clinical characteristics, including BMI, smoking history, menorrhagia, and presence of uterine fibroids. The demographic characteristics of the study population were representative of the regions covered by the participating healthcare systems as verified by comparison with census data.

COMMENT

The EURAS-IUD and APEX-IUD studies employ distinct and complementary designs to explore different research questions. EURAS-IUD recruited women across a 7-year period (2006-2012) to evaluate the risk of uterine perforation among IUD users in routine practice.[4] During 1 year of follow-up among 61,448 women, 81 uterine perforations were identified.[4] In a 5-year extension among 39,009 women, an additional 23 perforations were identified.[1] In comparison, protocol submission and initiation of data collection for APEX-IUD occurred in 2018; final results will be available within 20 months. In contrast, APEX-IUD provided up to 9.5 years of follow-up data, with over five times more women enrolled (a total of 326,658 US women), and it will be able to evaluate multiple additional potential risk factors for uterine perforation and IUD expulsion.

The APEX-IUD population was younger than the EURAS-IUD population[4]: mean age was 32.2 years versus 37.4 years among LNG IUD users and 31.2 years versus 33.3 years among copper IUD users. Across the four research sites, the APEX-IUD population reflected the general populations in the geographic regions from which they were drawn and was racially and ethnically diverse. The EURAS-IUD population included proportionally more smokers (23.2% current smokers) than APEX-IUD (10.2% who were smokers in the ≤12 months before IUD insertion) and proportionally more normal weight women with BMI <25 kg/m^2 (47.3% vs. 36.5% in APEX-IUD).

Clinical Implications

The APEX-IUD study will add to the information on IUD-related uterine perforation reported by EURAS-IUD investigators from a European population. APEX-IUD provides information

reflective of demographic characteristics and clinical care in the US. APEX-IUD, in addition, will include IUD expulsion as a study outcome and provide additional details regarding the impact of menorrhagia on outcomes. It will contribute significantly to knowledge about IUD risks that might lead to unintended pregnancy, providing a comprehensive picture that aids in clinical decision-making.

Research Implications

There are advantages to prospective cohort studies, including EURAS-IUD, such as the ability to specify the data to be collected, to query participants in real time, and to include those who might not be represented in healthcare data sources. However, prospective real-world studies rely on volunteers who might not completely reflect the populations of interest and require intensive follow-up procedures to ensure participant retention. APEX-IUD, as a US retrospective cohort study involving EHR data within insured health care systems, represents a satisfactory approach for a FDA-mandated study.

Strengths and Limitations

Key advantages of the APEX-IUD study are the retrospective design enabling a larger cohort, a shorter time to the availability of results, a longer duration of follow-up, and greater efficiency relative to a prospective design. Retrospective data collection from a healthcare system data source is limited to information about care received while enrolled in the healthcare system and assumes enrollees do not seek care outside of the system during their enrollment. Thus, risk estimates could be an underestimate of the outcomes. Results of this study depend on accurate capture of health information and definitions of variables selected. Misclassification is possible because variables were determined from codes and clinical notes (via NLP). There is also the

potential for misclassification of outcomes and risk factors within the data sources if women were not aware, did not seek treatment, or if treatment was not documented in an EHR.

Conclusion

This study has a large, socio-demographically diverse population with rich data providing the opportunity to evaluate the risk of uterine perforation and IUD expulsion in the setting of usual clinical practice in the US. Relative to a prospective study, the retrospective design of APEX-IUD enables a larger study population with a longer follow-up time and is a satisfactory alternative to an FDA request for prospective data. When reliable risk-factor, outcome, and covariates can be ascertained from the EHR, real-world data provide informative risk estimates that can be used to inform clinical practice. Future study results will provide valuable information based on real-world evidence about risk factors for IUD perforation and expulsion for clinicians.

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TABLES

Table 1. Association of Uterine Perforation and EXpulsion of IUD (APEX-IUD)

Study Variables

Variable	Definition	Categories	Format
Potential risk-factor variables			
Postpartum time of IUD insertion	Time since most recent delivery date ≤ index date[a]	▪ 0 to ≤3 days ▪ >3 days to ≤6 weeks ▪ >6 to ≤14 weeks ▪ >14 to ≤52 weeks ▪ >52 weeks or with no evidence of delivery	4 categories; 5 categories binary
Breastfeeding status	Breastfeeding status at index date[c,d,e]	▪ No ▪ Yes ▪ Undetermined[b]	3 categories
IUD type	IUD type at the time of the index date[d,e]	▪ LNG ▪ Copper ▪ Unknown	3 categories
Menorrhagia	Menorrhagia prior to or on index date[d]	▪ Yes, if diagnosis of menorrhagia within 12 months before the index date ▪ No, if no menorrhagia diagnosis within the 12 months before index date	Binary
Outcome variables			
Uterine perforation	Uterine perforation event during person-time at risk[d,e]	▪ Yes (partial, complete) ▪ No	Binary
IUD expulsion	IUD expulsion event during person-time at risk[d,e]	▪ Yes (partial, complete) ▪ No	Binary
Covariates			
Demographic			
Age	Age in years at IUD insertion[f]	▪ ≤28 years ▪ >28 to ≤36 years ▪ >36 to ≤50 years	Integer; 3 categories

Variable	Definition	Categories	Format
Race/ethnicity	Race/ethnicity[f]	▪ Asian/Pacific Islander ▪ Hispanic black ▪ Hispanic other ▪ Hispanic white ▪ Non-Hispanic black ▪ Non-Hispanic white ▪ Other or multiple ▪ Unknown	8 categories
Smoking	Smoked within 365 days of index date[c,d,e]	▪ No ▪ Yes ▪ Missing/Unknown	3 categories
Calendar year of IUD insertion	Calendar year of IUD insertion[d,e]	▪ 2001-2009 ▪ 2010 ▪ 2011 ▪ 2012 ▪ 2013 ▪ 2014 ▪ 2015 ▪ 2016 ▪ 2017 ▪ 2018	Categorical
Duration of lookback period	Duration of lookback period[a]	▪ ≥1 to ≤2 years ▪ >2 to ≤4 years ▪ >4 to ≤6.5 years ▪ >6.5 years Dichotomized: ▪ ≥1 to ≤4 years ▪ >4 years	Continuous; 4 categories; 2 categories
Clinical			
BMI	BMI (kg/m^2) at index date or closest date[d,e]	▪ Underweight (<18.5 kg/m^2) ▪ Normal weight (18.5-24.9 kg/m^2) ▪ Overweight (25.0-29.9 kg/m^2) ▪ Obesity (≥30.0 kg/m^2) ▪ Missing	Continuous; 5 categories

Variable	Definition	Categories	Format
Dysmenorrhea	Dysmenorrhea prior to or on index date[d]	▪ Diagnosis of dysmenorrhea within the 12 months before the index date but not diagnosed before that time ▪ No diagnosis of dysmenorrhea within the 12 months before the index date but a diagnosis of dysmenorrhea before that time ▪ Diagnosis of dysmenorrhea recorded both within the 12 months before the index date and before that time ▪ No diagnosis of dysmenorrhea found prior to or on the index date	4 categories
Menorrhagia	Menorrhagia prior to or on index date[d]	▪ Diagnosis of menorrhagia within the 12 months before the index date but not diagnosed before that time ▪ No diagnosis of menorrhagia within the 12 months before the index date but a diagnosis of menorrhagia before that time ▪ Diagnosis of menorrhagia recorded both within the 12 months before the index date and before that time ▪ No diagnosis of menorrhagia found prior to or on the index date	4 categories
Uterine fibroids	Fibroids prior to or on index date[d]	▪ No ▪ Yes	Binary
Parity	Cumulative number of viable pregnancies (i.e., carried to at least 20 weeks gestation) prior to the index date[d,e,f]	Dichotomized for analyses of IUD type and menorrhagia: ▪ 0 ▪ >0 Parity dichotomized for analyses of breastfeeding and postpartum period: ▪ ≤1 ▪ >1 Categorical: ▪ 0 ▪ 1 ▪ 2 ▪ ≥3 ▪ Missing	Integer; 2 categories; 2 categories; 5 categories

Variable	Definition	Categories	Format
Cesarean delivery	Any cesarean delivery during lookback period (summarized only if a woman had 1 or more parity)[d]	▪ No ▪ Yes	Binary
Cesarean for most recent delivery	Cesarean for most recent delivery (summarized only if there was a recorded delivery within 52 weeks prior to or on the index date)[d]	▪ No ▪ Yes	Binary
Concomitant gynecological procedure	Any of the following procedures at insertion[a]	▪ No ▪ Yes	Binary
Abortion procedure	Abortion[d]	▪ No ▪ Yes	Binary
Aspiration and curettage	Aspiration/curettage[d]	▪ No ▪ Yes	Binary
Dilation and curettage	Dilation and curettage[d]	▪ No ▪ Yes	Binary
Biopsy of cervix or uterus	Biopsy[d]	▪ No ▪ Yes	Binary
Ablation	Ablation[d]	▪ No ▪ Yes	Binary
Colposcopy and other cervical procedures	Colposcopy/cervical procedure[d]	▪ No ▪ Yes	Binary
Hysteroscopy procedure	Hysteroscopy at insertion[d]	▪ No ▪ Yes	Binary
Laminaria procedure	Laminaria[d]	▪ No ▪ Yes	Binary
Laparoscopy	Laparoscopy[d]	▪ No ▪ Yes	Binary
Lysis adhesions	Lysis adhesions[d]	▪ No ▪ Yes	Binary
Myomectomy	Myomectomy[d]	▪ No ▪ Yes	Binary
Nerve procedure	Nerve procedure[d]	▪ No ▪ Yes	Binary

Variable	Definition	Categories	Format
Salpingectomy/oophorectomy	Salpingectomy/ oophorectomy[d]	▪ No ▪ Yes	Binary
Indicator of a difficult IUD insertion	Any of the following indicators at insertion[a]	▪ No ▪ Yes	Binary
Dilation	Cervical dilation[d,e]	▪ No ▪ Yes	Binary
Ultrasound guidance	Ultrasound guidance[d,e]	▪ No ▪ Yes	Binary
Paracervical block	Paracervical block[d,e]	▪ No ▪ Yes	Binary
Provider noted difficult insertion	Provider noted difficult insertion[e]	▪ No ▪ Yes	Binary
Misoprostol	Misoprostol prior to insertion[d,e]	▪ No ▪ Yes	Binary
Clinician-related characteristics (available in KPNC, KPSC, and KPWA, not in RI)			
Number of IUD insertions performed	Number of IUD insertions performed[f]	▪ <50 insertions ▪ ≥50 insertions ▪ Missing	Continuous; 3 categories
Annualized number of insertions in previous year	Annualized number of insertions in previous year[a]	▪ 4 categories based on quartiles ▪ 2 categories based on median ▪ Missing	Continuous; 5 categories; 3 categories
Length of employment in previous year	Length of employment in previous year, in days[f]		Continuous and missing
Other			
Live birth	Live birth for the most recent delivery within the past 52 weeks of the index date (summarized only among women who had a delivery within 1 year before the index date)[d,f]	▪ No ▪ Yes	Binary

Variable	Definition	Categories	Format
Site	Study site[f]	▪ KPNC ▪ KPSC ▪ KPWA ▪ RI	4 Categories

BMI = body mass index; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; LNG = levonorgestrel; RI = Regenstrief Institute.

[a] Data source: Calculated.

[b] Those with no evidence of a delivery in the 52 weeks prior to index date were excluded from the breastfeeding analysis.

[c] Data source: Structured questionnaires.

[d] Data source: Codes.

[e] Data source: Natural language programming.

[f] Data source: Other sources.

433 **Table 2. Size of the Risk-Factor Groups, Pooled and by Research Site**

	Pooled (N = 326,658)	KPNC (n = 161,442)	KPSC (n = 123,214)	KPWA (n = 20,526)	RI (n = 21,476)
Person-years at risk	641,427	325,552	241,923	37,496	36,456
Characteristic					
Breastfeeding status (patients at ≤52 weeks postpartum), n (%)					
Yes	64,186 (65.6)	34,357 (74.8)	23,679 (57.7)	3,964 (68.1)	2,186 (43.8)
No	30,631 (31.3)	10,996 (23.9)	17,027 (41.5)	875 (15.0)	1,733 (34.7)
Undetermined (excluded)	3,007 (3.1)	578 (1.3)	363 (0.9)	986 (16.9)	1,080 (21.6)
Postpartum time of IUD insertion, n (%)					
0 to ≤3 days	2,788 (0.9)	2,001 (1.2)	106 (0.1)	27 (0.1)	654 (3.0)
>3 days to ≤6 weeks	17,272 (5.3)	10,615 (6.6)	4,818 (3.9)	747 (3.6)	1,092 (5.1)
>6 to ≤14 weeks	56,047 (17.2)	24,259 (15.0)	25,880 (21.0)	3,682 (17.9)	2,226 (10.4)
>14 to ≤52 weeks	21,717 (6.6)	9,056 (5.6)	10,265 (8.3)	1,369 (6.7)	1,027 (4.8)
>52 weeks or no delivery	228,834 (70.1)	115,511 (71.5)	82,145 (66.7)	14,701 (71.6)	16,477 (76.7)
Menorrhagia, n (%)					
≤12 months before insertion	32,552 (10.0)	13,593 (8.4)	15,727 (12.8)	2,027 (9.9)	1,205 (5.6)
>12 months or no diagnosis	294,106 (90.0)	147,849 (91.6)	107,487 (87.2)	18,499 (90.1)	20,271 (94.4)
Menorrhagia (patients at >52 weeks postpartum), n (%)					
≤12 months before insertion	31,600 (13.8)	13,204 (11.4)	15,297 (18.6)	1,961 (13.3)	1,138 (6.9)
>12 months or no diagnosis	197,234 (86.2)	102,307 (88.6)	66,848 (81.4)	12,740 (86.7)	15,339 (93.1)
IUD type, n (%)[a]					
LNG IUD	259,234 (79.4)	–	–	–	–
Copper IUD	63,664 (19.5)	–	–	–	–

	Pooled (N = 326,658)	KPNC (n = 161,442)	KPSC (n = 123,214)	KPWA (n = 20,526)	RI (n = 21,476)
Unknown	3,760 (1.2)	–	–	–	–

IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; LNG = levonorgestrel; RI = Regenstrief Institute.

[a] Site-specific results are not presented in keeping with data use agreements with Kaiser Permanente research sites.

Table 3. Percentages of Censoring Events, Pooled and by Research Site

Censoring Event	Pooled, %	KPNC, %	KPSC, %	KPWA, %	RI, %
Removal of IUD (single reason)	24.9	26.0	24.4	23.1	21.2
Subsequent IUD insertion (single reason)	1.4	0.8	1.9	2.0	2.2
Both removal and subsequent insertion	5.7	6.1	5.9	5.1	1.5
Pregnancy (single reason)	1.2	0.9	1.6	1.6	1.6
Hysterectomy (single reason)	0.4	0.1	0.7	0.5	0.8
Bilateral oophorectomy or other sterilization (single reason)	0.3	0.2	0.4	0.2	0.3
IUD expiration (single reason)[a]	4.5	4.8	4.1	4.4	3.7
Death (single reason)	0.1	0.1	0.1	<0.1	0.1
End of enrollment/follow-up (single reason)	25.6	23.7	26.1	43.6	20.2
End of study period (single reason)	32.0	32.8	31.2	16.6	45.2
Other multiple reasons recorded on the censoring date	0.9	1.0	0.7	0.4	1.4
Outcome event[b]	3.0	3.4	2.9	2.4	1.8
Total	100.0	100.0	100.0	100.0	100.0

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

[a] Added 3 months to the IUD expiration in the product label to allow for delayed medical appointments.

[b] May have had a censoring event(s) in addition to uterine perforation and/or IUD expulsion recorded on the same date.

Table 4. Average Length of Continuous Enrollment for the Study Population; Pooled and by Research Site

Characteristic	Pooled (N = 326,658)	KPNC (n = 161,442)	KPSC (n = 123,214)	KPWA (n = 20,526)	RI (n = 21,476)[a]
Continuous enrollment (months)					
Mean (SD)	88.6 (46.3)	81.3 (32.5)	83.5 (37.1)	81.0 (43.0)	180.0 (78.1)
Median (Q1, Q3)	90.0 (52.7, 114.0)	89.0 (52.0, 114.0)	85.0 (49.3, 126.0)	74.0 (44.0, 119.0)	176.8 (123.2, 230.4)
Min, max	12.0, 438.2	12.0, 114.0	12.0, 126.0	13.0, 150.0	12.0, 438.2
Continuous enrollment on or before index date (months)					
Mean (SD)	51.9 (42.0)	44.1 (25.8)	46.1 (28.7)	45.7 (31.1)	149.7 (77.2)
Median (Q1, Q3)	39.9 (23.1, 67.4)	37.5 (22.4, 61.0)	38.2 (22.4, 63.3)	36.0 (21.5, 60.9)	145.9 (89.4, 201.6)
Min, max	12.0, 435.2	12.0, 112.0	12.0, 124.0	12.1, 148.0	12.0, 435.2
Continuous enrollment on or after index date (months)					
Mean (SD)	36.8 (29.5)	37.3 (28.2)	37.4 (30.6)	35.4 (32.9)	30.3 (29.1)
Median (Q1, Q3)	28.7 (11.9, 57.1)	30.7 (13.0, 58.2)	28.5 (11.6, 58.6)	24.3 (9.5, 52.8)	21.8 (9.6, 39.0)
Min, max	0.0, 209.6	0.0, 101.9	0.0, 114.0	0.1, 137.9	0.0, 209.6

KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; Q1 = lower quartile (i.e., 25th percentile); Q3 = upper quartile (i.e., 75th percentile); RI = Regenstrief Institute; SD = standard deviation

[a] The data set used from RI does not contain enrollment date; first and last clinical counters were used.

Table 5. Characteristics of the Study Population at the Time of the First Observed IUD Insertion, Pooled and by Research Site

	Pooled (N = 326,658)	KPNC (n = 161,442)	KPSC (n = 123,214)	KPWA (n = 20,526)	RI (n = 21,476)
Person-years at risk	641,427	325,552	241,923	37,496	36,456
Characteristic					
Age (years)					
Mean (SD)	32.0 (8.3)	32.2 (8.3)	32.2 (8.3)	31.3 (8.2)	30.1 (8.0)
Categories, n (%)					
≤28 years	119,469 (36.6)	56,832 (35.2)	44,859 (36.4)	8,007 (39.0)	9,771 (45.5)
>28 to ≤36 years	107,871 (33.0)	54,047 (33.5)	39,915 (32.4)	7,042 (34.3)	6,867 (32.0)
>36 to ≤50 years	99,318 (30.4)	50,563 (31.3)	38,440 (31.2)	5,477 (26.7)	4,838 (22.5)
Race/ethnicity, n (%)					
Asian/Pacific Islander	38,911 (11.9)	26,216 (16.2)	9,998 (8.1)	2,122 (10.3)	575 (2.7)
Hispanic black	696 (0.2)	96 (0.1)	524 (0.4)	54 (0.3)	22 (0.1)
Hispanic other	56,180 (17.2)	33,967 (21.0)	21,284 (17.3)	716 (3.5)	213 (1.0)
Hispanic white	42,501 (13.0)	2,000 (1.2)	38,649 (31.4)	584 (2.8)	1,268 (5.9)
Non-Hispanic black	28,323 (8.7)	12,678 (7.9)	11,397 (9.2)	1,234 (6.0)	3,014 (14.0)
Non-Hispanic white	137,102 (42.0)	72,745 (45.1)	36,439 (29.6)	13,097 (63.8)	14,821 (69.0)
Other or multiple	16,357 (5.0)	12,249 (7.6)	2,913 (2.4)	492 (2.4)	703 (3.3)
Unknown	6,588 (2.0)	1,491 (0.9)	2,010 (1.6)	2,227 (10.8)	860 (4.0)
Recent smoker, n (%)					
Yes	32,623 (10.0)	14,929 (9.3)	11,288 (9.2)	1,680 (8.2)	4,726 (22.0)
No	288,539 (88.3)	144,366 (89.4)	110,831 (90.0)	16,592 (80.8)	16,750 (78.0)

	Pooled (N = 326,658)	KPNC (n = 161,442)	KPSC (n = 123,214)	KPWA (n = 20,526)	RI (n = 21,476)
Unknown/missing	5,496 (1.7)	2,147 (1.3)	1,095 (0.9)	2,254 (11.0)	0 (0.0)
BMI (kg/m^2)					
Mean (SD)	28.5 (7.0)	28.0 (6.8)	28.9 (7.0)	28.0 (7.1)	30.0 (8.2)
BMI Categories, n (%)					
Underweight	3,689 (1.1)	1,956 (1.2)	1,306 (1.1)	217 (1.1)	210 (1.0)
Normal weight	113,675 (34.8)	61,437 (38.1)	39,041 (31.7)	8,010 (39.0)	5,187 (24.2)
Overweight	96,181 (29.4)	47,887 (29.7)	37,631 (30.5)	5,638 (27.5)	5,025 (23.4)
Obese	107,674 (33.0)	49,371 (30.6)	44,925 (36.5)	6,011 (29.3)	7,367 (34.3)
Missing	5,439 (1.7)	791 (0.5)	311 (0.3)	650 (3.2)	3,687 (17.2)
Dysmenorrhea diagnosis, n (%)					
Recent (≤12 months before index only)	10,893 (3.3)	3,861 (2.4)	5,651 (4.6)	863 (4.2)	518 (2.4)
Past (>1 year before index only)	18,080 (5.5)	6,473 (4.0)	7,473 (6.1)	1,904 (9.3)	2,230 (10.4)
Diagnosis in recent and past periods	4,373 (1.3)	1,437 (0.9)	2,257 (1.8)	477 (2.3)	202 (0.9)
No diagnosis	293,312 (89.8)	149,671 (92.7)	107,833 (87.5)	17,282 (84.2)	18,526 (86.3)
Menorrhagia diagnosis, n (%)					
Recent (≤12 months before index only)	23,398 (7.2)	10,373 (6.4)	10,826 (8.8)	1,362 (6.6)	837 (3.9)
Past (>1 year before index only)	13,288 (4.1)	4,698 (2.9)	5,501 (4.5)	1,343 (6.5)	1,746 (8.1)
Diagnosis in recent and past periods	9,154 (2.8)	3,220 (2.0)	4,901 (4.0)	665 (3.2)	368 (1.7)
No diagnosis	280,818 (86.0)	143,151 (88.7)	101,986 (82.8)	17,156 (83.6)	18,525 (86.3)
Fibroid diagnosis, n (%)	17,416 (5.3)	7,742 (4.8)	8,096 (6.6)	1,271 (6.2)	307 (1.4)
Parity, n (%)					

	Pooled (N = 326,658)	KPNC (n = 161,442)	KPSC (n = 123,214)	KPWA (n = 20,526)	RI (n = 21,476)
0	61,920 (19.0)	36,814 (22.8)	18,980 (15.4)	3,973 (19.4)	2,153 (10.0)
>0	225,925 (69.2)	112,478 (69.7)	95,495 (77.5)	8,161 (39.8)	9,791 (45.6)
Missing	38,813 (11.9)	12,150 (7.5)	8,739 (7.1)	8,392 (40.9)	9,532 (44.4)
Cesarean delivery any time before the index date, n (%)					
Yes	54,295 (16.6)	25,233 (15.6)	22,939 (18.6)	2,295 (11.2)	3,828 (17.8)
No	171,630 (52.5)	87,245 (54.0)	72,556 (58.9)	5,866 (28.6)	5,963 (27.8)
Nullipara or missing, n	100,733 (30.8)	48,964 (30.3)	27,719 (22.5)	12,365 (60.2)	11,685 (54.4)
Cesarean delivery at most recent delivery before the index date					
Yes, n (%)	23,245 (7.1)	10,081 (6.2)	10,638 (8.6)	1,402 (6.8)	1,124 (5.2)
No, n (%)	74,579 (22.8)	35,850 (22.2)	30,431 (24.7)	4,423 (21.6)	3,875 (18.0)
No delivery in past year, n	228,834 (70.1)	115,511 (71.6)	82,145 (66.7)	14,701 (71.6)	16,477 (76.7)
Concomitant gynecological procedure					
Yes[a], n (%)	26,234 (8.0)	13,494 (8.4)	10,770 (8.7)	1,275 (6.2)	695 (3.2)
Difficult insertion indicator, n (%)					
Any difficult insertion	29,777 (9.1)	19,685 (12.2)	4,273 (3.5)	2,324 (11.3)	3,495 (16.3)
Cervical dilation	10,209 (3.1)	8,501 (5.3)	33 (0.0)	102 (0.5)	1,573 (7.3)
Ultrasound guidance	4,628 (1.4)	3,620 (2.2)	252 (0.2)	194 (0.9)	562 (2.6)
Paracervical block	14,731 (4.5)	12,788 (7.9)	1,051 (0.9)	654 (3.2)	238 (1.1)
Difficult insertion noted	2,987 (0.9)	1,701 (1.1)	767 (0.6)	230 (1.1)	289 (1.3)
Use of misoprostol	8,689 (2.7)	3,827 (2.4)	2,329 (1.9)	1,295 (6.3)	1,238 (5.8)
Calendar year of IUD insertion, n (%)					
2001-2009	16,524 (5.1)	0	10,840 (8.8)	4,585 (22.3)	1,099 (5.1)
2010	31,563 (9.7)	18,206 (11.3)	11,032 (9.0)	1,847 (9.0)	478 (2.2)

	Pooled (N = 326,658)	KPNC (n = 161,442)	KPSC (n = 123,214)	KPWA (n = 20,526)	RI (n = 21,476)
2011	32,747 (10.0)	17,974 (11.1)	12,311 (10.0)	1,986 (9.7)	476 (2.2)
2012	36,584 (11.2)	19,911 (12.3)	13,728 (11.1)	2,111 (10.3)	834 (3.9)
2013	34,303 (10.5)	18,694 (11.6)	12,377 (10.0)	2,012 (9.8)	1,220 (5.7)
2014	33,946 (10.4)	18,769 (11.6)	11,699 (9.5)	1,963 (9.6)	1,515 (7.1)
2015	37,621 (11.5)	19,144 (11.9)	13,072 (10.6)	2,006 (9.8)	3,399 (15.8)
2016	41,302 (12.6)	20,242 (12.5)	14,894 (12.1)	1,773 (8.6)	4,393 (20.5)
2017	46,518 (14.2)	21,688 (13.4)	17,284 (14.0)	1,681 (8.2)	5,865 (27.3)
2018	15,550 (4.8)	6,814 (4.2)	5,977 (4.9)	562 (2.7)	2,197 (10.2)
Duration of lookback period (months)					
Mean (SD)	56.8 (42.3)	53.9 (28.7)	46.1 (28.7)	45.7 (31.1)	149.7 (77.2)
Min, max	12, 435	12, 112	12, 124	12, 148	12, 435

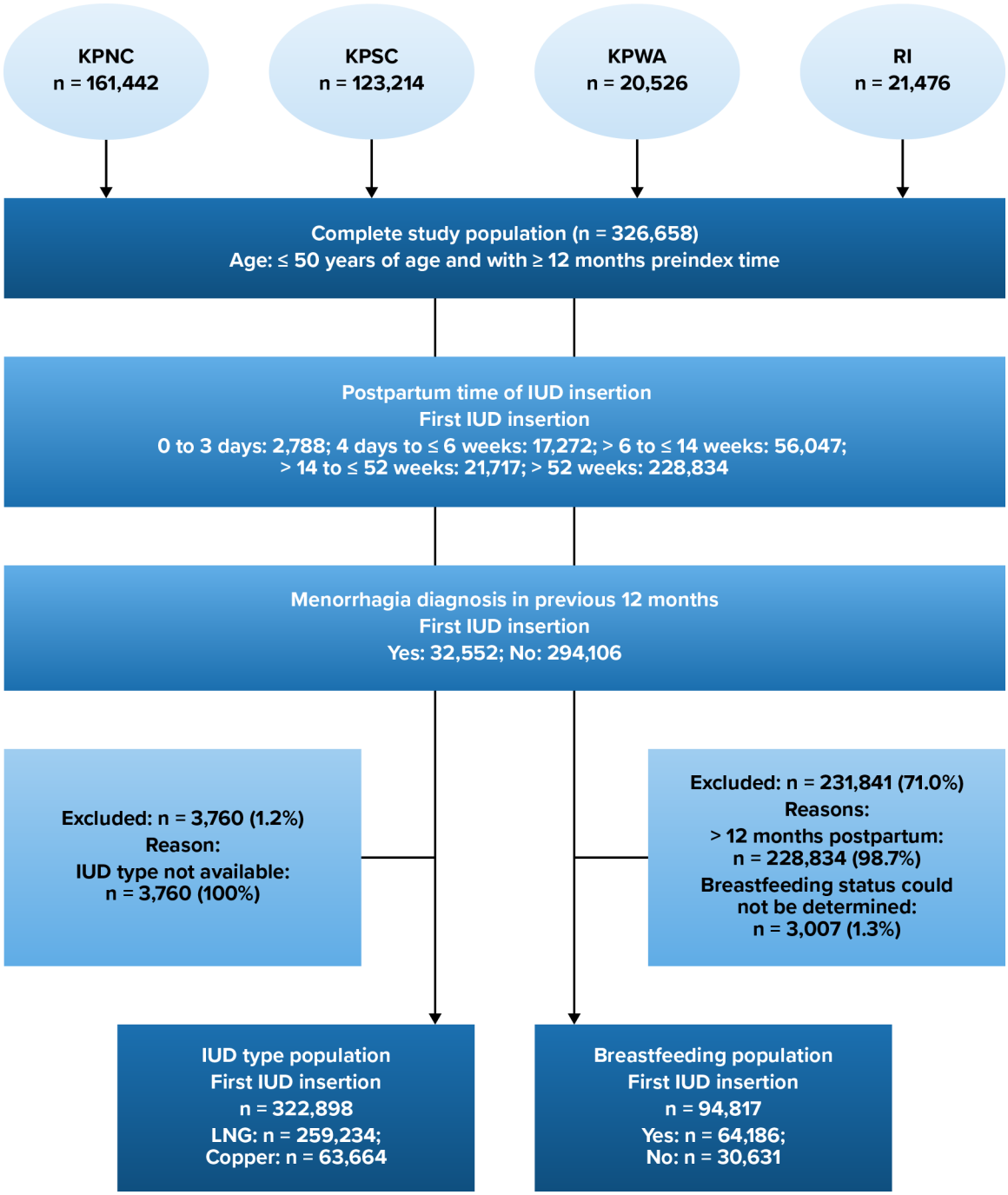
BMI = body mass index; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute; SD = standard deviation; min = minimum; max = maximum.

[a] At least one of the following: abortion, aspiration and curettage, dilation and curettage, excision/biopsy of cervix or uterus, ablation, colposcopy and other cervical procedures, hysteroscopy procedure, laminaria procedure, laparoscopy, lysis adhesions, myomectomy, nerve procedure, salpingectomy/oophorectomy.

FIGURE LEGEND

Figure 1. Study Populations, Exclusions, and Number of First Observed IUD Insertions in Risk-Factor Groups

IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute; wks = weeks.


KPNC
n = 161,442
KPSC
n = 123,214
KPWA
n = 20,526
RI
n = 21,476
Complete study population (n = 326,658)
Age: ≤ 50 years of age and with ≥ 12 months preindex time
Postpartum time of IUD insertion
First IUD insertion
0 to 3 days: 2,788; 4 days to ≤ 6 weeks: 17,272; > 6 to ≤ 14 weeks: 56,047;
> 14 to ≤ 52 weeks: 21,717; > 52 weeks: 228,834
Menorrhagia diagnosis in previous 12 months
First IUD insertion
Yes: 32,552; No: 294,106
Excluded: n = 3,760 (1.2%)
Reason:
IUD type not available:
n = 3,760 (100%)
Excluded: n = 231,841 (71.0%)
Reasons:
> 12 months postpartum:
n = 228,834 (98.7%)
Breastfeeding status could
not be determined:
n = 3,007 (1.3%)
IUD type population
First IUD insertion
n = 322,898
LNG: n = 259,234;
Copper: n = 63,664
Breastfeeding population
First IUD insertion
n = 94,817
Yes: n = 64,186;
No: n = 30,631