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Design of the Association of Uterine Perforation and Expulsion of Intrauterine Device study: a multisite retrospective cohort study

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BACKGROUND: Intrauterine devices are effective and safe, long-acting reversible contraceptives, but the risk of uterine perforation occurs with an estimated incidence of 1 to 2 per 1000 insertions. The European Active Surveillance Study for Intrauterine Devices, 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 at ≤36 weeks after delivery had a higher risk of uterine perforation. The Association of Uterine Perforation and Expulsion of Intrauterine Device (APEX-IUD) study was a Food and Drug Administration–mandated study designed to reflect current United States clinical practice. The aims of the APEX-IUD study were to evaluate the risk of intrauterine device–related uterine perforation and device expulsion among women who were breastfeeding or within 12 months after delivery at insertion.

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

STUDY DESIGN: APEX-IUD study was a retrospective cohort study conducted in 4 organizations with access to electronic health records: Kaiser Permanente Northern California, Kaiser Permanente Southern California, Kaiser Permanente Washington, and Regenstrief Institute in Indiana. Variables were identified through structured data (eg, diagnostic, procedural, medication codes) and unstructured data (eg, clinical notes) via natural language processing. Outcomes include uterine perforation and device expulsion; potential risk factors were breastfeeding at insertion, postpartum timing of insertion, device type, and menorrhagia diagnosis in the year before 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 (from January 1, 2001 to January 1, 2010). Follow-up begins at insertion and ends at first occurrence of an outcome of interest, a censoring event (device removal or reinsertion, pregnancy, hysterectomy, sterilization, device expiration, death, disenrollment, last clinical encounter), or end of the study period (June 30, 2018). Comparisons of levels of exposure variables were 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 1 device insertion during the study period (Kaiser Permanente Northern California, 161,442; Kaiser Permanente Southern California, 123,214; Kaiser Permanente Washington, 20,526; Regenstrief Institute, 21,476). The median duration of continuous enrollment was 90 (site medians 74–177) months. The mean age was 32 years, and the population was racially and ethnically diverse across the 4 sites. The mean body mass index was 28.5 kg/m^2, and of the women included in the study, 10.0% had menorrhagia ≤12 months before insertion, 5.3% had uterine fibroids, and 10% were recent smokers; furthermore, among these women, 79.4% had levonorgestrel-releasing devices, and 19.5% had copper devices. Across sites, 97,824 women had an intrauterine device insertion at ≤52 weeks after delivery, of which 94,817 women (97%) had breastfeeding status at insertion determined; in addition, 228,834 women had intrauterine device insertion at >52 weeks after delivery 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 the APEX-IUD study results reflect current United States clinical practice. Results from this study will provide valuable information based on real-world evidence about risk factors for intrauterine devices perforation and expulsion for clinicians.

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

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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 to 2 perforations per 1000 insertions.[2,3] These rates were reported in 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 6 European countries, with recruitment from 2006 to 2012.[4] Here, 2 cohorts were included: new users of LNG-releasing IUDs (n=43,078) or

AJOG at a Glance

Why was this study conducted?

The European Active Surveillance Study for Intrauterine Devices showed an increased risk of uterine perforation among women who were breastfeeding or ≤36 weeks after delivery at intrauterine device (IUD) insertion. The US Food and Drug Administration suspected differences in breastfeeding practices and postpartum timing of IUD placement and mandated a study to assess risks among women in the United States.

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.

What does this add to what is 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 the risk of perforation and expulsion.

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 the relative risk of uterine perforation. Furthermore, there was 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 after delivery, a more accepted practice in the United States.[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 the 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 Association of Uterine Perforation and Expulsion of IUD (APEX-IUD) study was planned in coordination with Bayer and the FDA.

The APEX-IUD study was a multisite, retrospective cohort study that used data from EHRs and a health information exchange to assess 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 describes the study design, methodology, and characteristics of the study population. In addition, comparisons with the methods of the prospective cohort study, EURAS-IUD, are discussed. The study results of the APEX-IUD study 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]). Here, the first potential date for a woman's inclusion varied by research site based in part on when EHR data became available at the beginning of the year at each site, 2001 at the RI, 2007 at 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 was on April 30, 2018. All IUD insertions from eligible women have been included.

Study design

The APEX-IUD study was a retrospective cohort study. Among women with an IUD insertion identified within EHR data, this study has evaluated the association of 2 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 (ie, the data were abstracted from patient care records rather than data collected for a clinical trial). In addition, the association of 2 secondary potential risk factors, recent history of menorrhagia and IUD type, and said outcomes were evaluated. Women were observed from IUD insertion date (index date) to the earliest date of IUD-related uterine perforation, IUD expulsion, IUD removal, IUD reinsertion, pregnancy, hysterectomy or other sterilization procedures, 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 data were included with no requirement for minimum or maximum follow-up time.

All participating research sites received an approval or a waiver to conduct this study from their respective institutional review boards. In addition, KPSC received approval from the California Health and Human Services Agency and the California Department of Public Health Center for Health Statistics and Informatics (state birth and death files). Each site submitted data for analysis in a deidentified, standard format in

TABLE 1
The Association of Uterine Perforation and Expulsion of 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−≤3 d ■ >3 d−≤6 wk ■ >6−≤14 wk ■ >14−≤52 wk ■ >52 wk or with no evidence of delivery	4 categories; 5 categories; binary
Breastfeeding status	Breastfeeding status at index date[b,c,d]	■ No ■ Yes ■ Undetermined[e]	3 categories
IUD type	IUD type at the time of the index date[c,d]	■ LNG ■ Copper ■ Unknown	3 categories
Menorrhagia	Menorrhagia before or on index date[c]	■ Yes, if diagnosis of menorrhagia within 12 mo before the index date ■ No, if no menorrhagia diagnosis within the 12 mo before index date	Binary
Outcome variables			
Uterine perforation	Uterine perforation event during person-time at risk[c,d]	■ Yes (partial, complete) ■ No	Binary
IUD expulsion	IUD expulsion event during person-time at risk[c,d]	■ Yes (partial, complete) ■ No	Binary
Covariates			
Demographic			
Age	Age in years at IUD insertion[f]	■ ≤28 y ■ >28−≤36 y ■ >36−≤50 y	Integer; 3 categories
Race and ethnicity	Race and ethnicity[f]	■ Asian or Pacific Islander ■ Hispanic Black ■ Hispanic other ■ Hispanic White ■ Non-Hispanic Black ■ Non-Hispanic White ■ Other or multiple ■ Unknown	8 categories
Smoking	Smoked within 365 d of index date[b,c,d]	■ No ■ Yes ■ Missing or unknown	3 categories

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(continued)

TABLE 1
The Association of Uterine Perforation and Expulsion of IUD study variables *(continued)*

Variable	Definition	Categories	Format
Calendar year of IUD insertion	Calendar year of IUD insertion[c,d]	■ 2001–2009 ■ 2010 ■ 2011 ■ 2012 ■ 2013 ■ 2014 ■ 2015 ■ 2016 ■ 2017 ■ 2018	Categorical
Duration of lookback period	Duration of lookback period[a]	■ ≥1–≤2 y ■ >2–≤4 y ■ >4–≤6.5 y ■ >6.5 y Dichotomized: ■ ≥1–≤4 y ■ >4 y	Continuous; 4 categories; 2 categories
Clinical			
BMI	BMI (kg/m^2) at index date or closest date[c,d]	■ 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
Dysmenorrhea	Dysmenorrhea before or on index date[c]	■ Diagnosis of dysmenorrhea within the 12 mo before the index date but not diagnosed before that time ■ No diagnosis of dysmenorrhea within the 12 mo before the index date but a diagnosis of dysmenorrhea before that time ■ Diagnosis of dysmenorrhea recorded both within the 12 mo before the index date and before that time ■ No diagnosis of dysmenorrhea found before or on the index date	4 categories

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TABLE 1
The Association of Uterine Perforation and Expulsion of IUD study variables *(continued)*

Variable	Definition	Categories	Format
Menorrhagia	Menorrhagia before or on index date[c]	■ Diagnosis of menorrhagia within the 12 mo before the index date but not diagnosed before that time ■ No diagnosis of menorrhagia within the 12 mo before the index date but a diagnosis of menorrhagia before that time ■ Diagnosis of menorrhagia recorded both within the 12 mo before the index date and before that time ■ No diagnosis of menorrhagia found before or on the index date	4 categories
Uterine fibroids	Fibroids before or on index date[c]	■ No ■ Yes	Binary
Parity	Cumulative number of viable pregnancies (ie, carried to at least 20 wk gestation) before the index date[c,d,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
Cesarean delivery	Any cesarean delivery during the lookback period (summarized only if a woman had one or more parity)[c]	■ No ■ Yes	Binary
Cesarean delivery for most recent delivery	Cesarean delivery for most recent delivery (summarized only if there was a recorded delivery within 52 wk before or on the index date)[c]	■ No ■ Yes	Binary
Concomitant gynecologic procedure	Any of the following procedures at insertion[a]	■ No ■ Yes	Binary
Abortion procedure	Abortion[c]	■ No ■ Yes	Binary
Aspiration and curettage	Aspiration and curettage[c]	■ No ■ Yes	Binary
Dilation and curettage	Dilation and curettage[c]	■ No ■ Yes	Binary

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TABLE 1
The Association of Uterine Perforation and Expulsion of IUD study variables *(continued)*

Variable	Definition	Categories	Format
Biopsy of the cervix or uterus	Biopsy[c]	■ No ■ Yes	Binary
Ablation	Ablation[c]	■ No ■ Yes	Binary
Colposcopy and other cervical procedures	Colposcopy and cervical procedures[c]	■ No ■ Yes	Binary
Hysteroscopy procedure	Hysteroscopy at insertion[c]	■ No ■ Yes	Binary
Laminaria procedure	Laminaria[c]	■ No ■ Yes	Binary
Laparoscopy	Laparoscopy[c]	■ No ■ Yes	Binary
Lysis adhesions	Lysis adhesions[c]	■ No ■ Yes	Binary
Myomectomy	Myomectomy[c]	■ No ■ Yes	Binary
Nerve procedure	Nerve procedure[c]	■ No ■ Yes	Binary
Salpingectomy or oophorectomy	Salpingectomy or oophorectomy[c]	■ No ■ Yes	Binary
Indicator of a difficult IUD insertion	Any of the following indicators at insertion[a]	■ No ■ Yes	Binary
Dilation	Cervical dilation[c,d]	■ No ■ Yes	Binary
Ultrasound guidance	Ultrasound guidance[c,d]	■ No ■ Yes	Binary
Paracervical block	Paracervical block[c,d]	■ No ■ Yes	Binary
Provider noted difficult insertion	Provider noted difficult insertion[d]	■ No ■ Yes	Binary
Misoprostol	Misoprostol before insertion[c,d]	■ No ■ Yes	Binary

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(continued)

TABLE 1
The Association of Uterine Perforation and Expulsion of IUD study variables *(continued)*

Variable	Definition	Categories	Format
Clinician-related characteristics (available in KPNC, KPSC, and KPWA but 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 wk of the index date (summarized only among women who had a delivery within 1 y before the index date)[c,f]	■ No ■ Yes	Binary
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] Data source: structured questionnaires; [c] Data source: codes; [d] Data source: natural language programming; [e] Those with no evidence of a delivery in the 52 weeks before index date were excluded from the breastfeeding analysis; [f] Data source: other sources.

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accordance with the data structure template for variables (Table 1).

Data sources

Data were obtained from 3 integrated healthcare systems with EHRs (KPNC, KPSC, and KPWA) and the RI, an organization with research access to a health information exchange with access to EHRs. These study sites were included on the basis of their ability to access population-based EHR data, data quality, and variation in demographics. Appendix A provides additional detail.

Potential risk factors, covariates, and outcomes were identified from the EHRs and included both structured data (eg, International Classification of Diseases, Ninth Revision, or International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-9 or ICD-10-CM] diagnosis and procedure codes, medication codes, Current Procedural Terminology codes, and Healthcare Common Procedural Coding System codes) and unstructured data (eg, clinical notes). Algorithms were developed to identify potential risk factors and outcomes using operational definitions, natural language processing (NLP), and medical record 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 owing to the 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 while ICD-9-CM codes were in use, prior to use of ICD-10-CM coding. The proportions of women at risk who had 1 of these outcomes were calculated and compared before and after the implementation of ICD-10-CM coding to assess temporal consistency over coding terms (Appendix B).

Potential risk factors

Two primary risk factors were evaluated: time of IUD insertion after delivery and breastfeeding status at time of IUD insertion. Postpartum time of IUD

insertion, originally categorized into 4 discrete periods in agreement with FDA, was later expanded to 5 periods, 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 to 52 weeks after delivery), "no" (last breastfeeding date >30 days before IUD insertion or first nonbreastfeeding date before IUD insertion), or "undetermined." Women with undetermined breastfeeding status were excluded from the breastfeeding cohort analyses. Other key potential risk factors included 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 were assessed: (1) uterine perforation, defined as complete perforation (with clinical evidence of IUD in the pelvis or abdominal cavity) or partial perforation (ie, 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 the RI, KPNC, and KPWA, potential uterine perforations identified by structured and unstructured data were confirmed using medical record review.

Covariates

Demographic and clinical characteristics were assessed before the index date for each eligible IUD insertion. All available data, but a minimum of 12 months before the index date, were used to evaluate women's characteristics and potential confounders, thus reducing the misclassification of demographic and clinical characteristics.[7] Demographic covariates included age, self-reported race and ethnicity and smoking status, month and year of the index date, and duration of the lookback period; clinical covariates included 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 (eg, concomitant gynecologic procedure) and clinician-related covariates (eg, number of IUD insertions in the previous year) were also collected (Table 1).

Study variables

For the outcome evaluations, person-time at risk was calculated from the IUD insertion date to the first occurrence of an outcome or censoring date, at which point follow-up ends for that outcome. The censoring date was 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 using PASS 14 software (NCSS Statistical Software, Kaysville, UT) for a 2-sided test of the hazard ratio (HR).[8] Because IUD expulsion rates are higher than uterine perforation rates, the 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 (SD), minimum, maximum, median, and quartiles were computed. Missing data were treated as missing, and no imputation was performed. All analyses were performed using Statistical Analysis System (SAS) software, (version 9.3 or higher; SAS Institute, Inc, Cary, NC).

Crude incidence rates and cumulative incidence of the outcomes will be estimated for each risk factor group (eg, 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 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 overlap weighting method[9] is used which has an advantage of not requiring trimming of observations; furthermore, observations with significant overlap between groups will be up-weighted, and observations with very little overlap will be down-weighted, compared with regular inverse probability treatment weighting. To assess whether covariates are balanced across risk factor groups after weighting, the distribution of each variable will be compared between categories of the risk factor variable, and balance parameters (ie, standardized differences) will be calculated.[10] Appendix C provides additional detail.

TABLE 2
Size of the risk factor groups, pooled and by research site

Variable	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 wk postpartum)					
Yes	64,186 (65.6)	34,357 (74.8)	23,679 (57.7)	3964 (68.1)	2186 (43.8)
No	30,631 (31.3)	10,996 (23.9)	17,027 (41.5)	875 (15.0)	1733 (34.7)
Undetermined (excluded)	3007 (3.1)	578 (1.3)	363 (0.9)	986 (16.9)	1080 (21.6)
Postpartum time of IUD insertion					
0−≤3 d	2788 (0.9)	2001 (1.2)	106 (0.1)	27 (0.1)	654 (3.0)
>3 d−≤6 wk	17,272 (5.3)	10,615 (6.6)	4818 (3.9)	747 (3.6)	1092 (5.1)
>6−≤14 wk	56,047 (17.2)	24,259 (15.0)	25,880 (21.0)	3682 (17.9)	2226 (10.4)
>14−≤52 wk	21,717 (6.6)	9056 (5.6)	10,265 (8.3)	1369 (6.7)	1027 (4.8)
>52 wk or no delivery	228,834 (70.1)	115,511 (71.5)	82,145 (66.7)	14,701 (71.6)	16,477 (76.7)
Menorrhagia					
≤12 mo before insertion	32,552 (10.0)	13,593 (8.4)	15,727 (12.8)	2027 (9.9)	1205 (5.6)
>12 mo 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 wk after delivery)					
≤12 mo before insertion	31,600 (13.8)	13,204 (11.4)	15,297 (18.6)	1961 (13.3)	1138 (6.9)
>12 mo 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[a]					
LNG-IUD	259,234 (79.4)	—	—	—	—
Copper IUD	63,664 (19.5)	—	—	—	—
Unknown	3,760 (1.2)	—	—	—	—

Data are presented as number (percentage).

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.

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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 included 326,658 women with at least 1 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 only reflects the first IUD insertion.

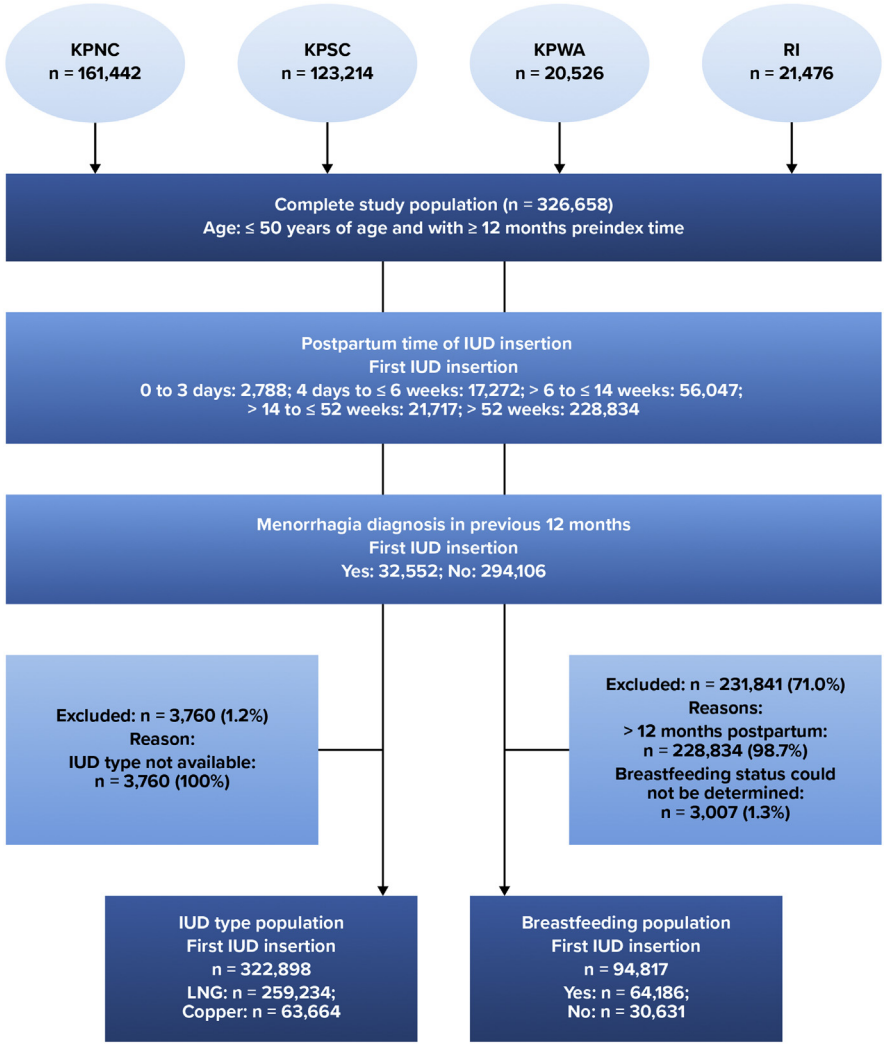
Size of risk factor groups

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) compared with women not breastfeeding (n=30,631) (Table 2; Figure). Most women (228,834 of 326,658) had an IUD placement more than 52 weeks after delivery or had no evidence of a delivery in their EHR. At the time of the first identified IUD insertion, 10% of women (range across sites, 5.6%−12.8%) 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 IUD type was not available (approximately 1%).

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 the study period (32.0%), and end of enrollment or follow-up (25.6%) accounted for most censoring events (89.6%). The proportion of censoring because of IUD expiration, the approach

FIGURE
Schematic of study population and risk factor groups



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

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used if no other censoring event or outcome occurred before this time, was 4.5%. Across all sites, the 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 shows the demographics and characteristics of the study population stratified by research site. The mean age in this population was 32 years, and the population was racially and ethnically diverse across the 4 sites. Mean BMI was 28.5 kg/m^2 (SD, 7.0 kg/m^2); 10% of women were recent smokers. Population characteristics were generally well balanced across sites, with some variations 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 employed distinct and complementary designs to explore different research questions. The EURAS-IUD recruited women over 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.[2] In comparison, protocol submission and initiation of data collection for the APEX-IUD study occurred in 2018; final results will be available after 20 months. Also the APEX-IUD study provided up to 9.5 years of follow-up data, with more than 5 times more women enrolled (a total of 326,658 women in the United States), and the study evaluated 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 vs 37.4 years among LNG-IUD users and 31.2 years vs 33.3 years among copper IUD users. Across the 4 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 the APEX-IUD population (10.2% who were smokers in ≤12 months before IUD insertion) and proportionally more women with normal weight as evidence by a BMI of <25 kg/m^2 (47.3% vs 36.5% in the APEX-IUD population).

Clinical implications

The APEX-IUD study will provide additional information on IUD-related uterine perforation reported by EURAS-IUD investigators from a European population. The APEX-IUD study provides information reflective of demographic characteristics and clinical care in the United States. In

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 or follow-up (single reason)	25.6	23.7	26.1	43.6	20.2
End of the 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 events in addition to uterine perforation and/or IUD expulsion recorded on the same date.

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addition, the APEX-IUD study will include IUD expulsion as a study outcome and provide additional details regarding the impact of menorrhagia on outcomes. The study will contribute significantly to the knowledge regarding 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 the EURAS-IUD, such as the ability to specify the data to be collected, to query participants

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 (mo)					
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 (mo)					
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 (mo)					
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; *min*, minimum; *max*, maximum; *Q1*, lower quartile (ie, 25th percentile); *Q3*, upper quartile (ie, 75th percentile); *RI*, Regenstrief Institute; *SD*, standard deviation.

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

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TABLE 5
Characteristics of the study population at the time of the first observed intrauterine device insertion, pooled and by research site

Variables	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 (y)					
Mean (SD)	32.0 (8.3)	32.2 (8.3)	32.2 (8.3)	31.3 (8.2)	30.1 (8.0)
Categories					
≤28 y	119,469 (36.6)	56,832 (35.2)	44,859 (36.4)	8007 (39.0)	9771 (45.5)
>28–≤36 y	107,871 (33.0)	54,047 (33.5)	39,915 (32.4)	7042 (34.3)	6867 (32.0)
>36–≤50 y	99,318 (30.4)	50,563 (31.3)	38,440 (31.2)	5477 (26.7)	4838 (22.5)
Race and ethnicity					
Asian or Pacific Islander	38,911 (11.9)	26,216 (16.2)	9998 (8.1)	2122 (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)	2000 (1.2)	38,649 (31.4)	584 (2.8)	1268 (5.9)
Non-Hispanic Black	28,323 (8.7)	12,678 (7.9)	11,397 (9.2)	1234 (6.0)	3014 (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)	2913 (2.4)	492 (2.4)	703 (3.3)
Unknown	6588 (2.0)	1491 (0.9)	2010 (1.6)	2227 (10.8)	860 (4.0)
Recent smoker					
Yes	32,623 (10.0)	14,929 (9.3)	11,288 (9.2)	1680 (8.2)	4726 (22.0)
No	288,539 (88.3)	144,366 (89.4)	110,831 (90.0)	16,592 (80.8)	16,750 (78.0)
Unknown or missing	5496 (1.7)	2147 (1.3)	1095 (0.9)	2254 (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					
Underweight	3689 (1.1)	1956 (1.2)	1306 (1.1)	217 (1.1)	210 (1.0)
Normal weight	113,675 (34.8)	61,437 (38.1)	39,041 (31.7)	8010 (39.0)	5187 (24.2)
Overweight	96,181 (29.4)	47,887 (29.7)	37,631 (30.5)	5638 (27.5)	5025 (23.4)
Obese	107,674 (33.0)	49,371 (30.6)	44,925 (36.5)	6011 (29.3)	7367 (34.3)
Missing	5439 (1.7)	791 (0.5)	311 (0.3)	650 (3.2)	3687 (17.2)
Dysmenorrhea diagnosis					
Recent (≤12 mo before index only)	10,893 (3.3)	3861 (2.4)	5651 (4.6)	863 (4.2)	518 (2.4)
Past (>1 y before index only)	18,080 (5.5)	6473 (4.0)	7473 (6.1)	1904 (9.3)	2230 (10.4)
Diagnosis in recent and past periods	4373 (1.3)	1437 (0.9)	2257 (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)

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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. As a US retrospective cohort study involving EHR data within insured healthcare systems, the APEX-IUD study represents a satisfactory approach for an FDA-mandated study.

TABLE 5
Characteristics of the study population at the time of the first observed intrauterine device insertion, pooled and by research site *(continued)*

Variables	Pooled (N=326,658)	KPNC (n=161,442)	KPSC (n=123,214)	KPWA (n=20,526)	RI (n=21,476)
Menorrhagia diagnosis					
Recent (≤12 mo before index only)	23,398 (7.2)	10,373 (6.4)	10,826 (8.8)	1362 (6.6)	837 (3.9)
Past (>1 y before index only)	13,288 (4.1)	4698 (2.9)	5501 (4.5)	1343 (6.5)	1746 (8.1)
Diagnosis in recent and past periods	9154 (2.8)	3220 (2.0)	4901 (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	17,416 (5.3)	7742 (4.8)	8096 (6.6)	1271 (6.2)	307 (1.4)
Parity					
0	61,920 (19.0)	36,814 (22.8)	18,980 (15.4)	3973 (19.4)	2153 (10.0)
>0	225,925 (69.2)	112,478 (69.7)	95,495 (77.5)	8161 (39.8)	9791 (45.6)
Missing	38,813 (11.9)	12,150 (7.5)	8739 (7.1)	8392 (40.9)	9532 (44.4)
Cesarean delivery any time before the index date					
Yes	54,295 (16.6)	25,233 (15.6)	22,939 (18.6)	2295 (11.2)	3828 (17.8)
No	171,630 (52.5)	87,245 (54.0)	72,556 (58.9)	5866 (28.6)	5963 (27.8)
Nullipara or missing	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	23,245 (7.1)	10,081 (6.2)	10,638 (8.6)	1402 (6.8)	1124 (5.2)
No	74,579 (22.8)	35,850 (22.2)	30,431 (24.7)	4423 (21.6)	3875 (18.0)
No delivery in past year	228,834 (70.1)	115,511 (71.6)	82,145 (66.7)	14,701 (71.6)	16,477 (76.7)
Concomitant gynecologic procedure					
Yes[a]	26,234 (8.0)	13,494 (8.4)	10,770 (8.7)	1275 (6.2)	695 (3.2)
Difficult insertion indicator					
Any difficult insertion	29,777 (9.1)	19,685 (12.2)	4273 (3.5)	2324 (11.3)	3495 (16.3)
Cervical dilation	10,209 (3.1)	8501 (5.3)	33 (0.0)	102 (0.5)	1573 (7.3)
Ultrasound guidance	4628 (1.4)	3620 (2.2)	252 (0.2)	194 (0.9)	562 (2.6)
Paracervical block	14,731 (4.5)	12,788 (7.9)	1051 (0.9)	654 (3.2)	238 (1.1)
Difficult insertion noted	2987 (0.9)	1701 (1.1)	767 (0.6)	230 (1.1)	289 (1.3)
Use of misoprostol	8689 (2.7)	3827 (2.4)	2329 (1.9)	1295 (6.3)	1238 (5.8)
Calendar year of IUD insertion					
2001–2009	16,524 (5.1)	0	10,840 (8.8)	4585 (22.3)	1099 (5.1)
2010	31,563 (9.7)	18,206 (11.3)	11,032 (9.0)	1847 (9.0)	478 (2.2)
2011	32,747 (10.0)	17,974 (11.1)	12,311 (10.0)	1986 (9.7)	476 (2.2)
2012	36,584 (11.2)	19,911 (12.3)	13,728 (11.1)	2111 (10.3)	834 (3.9)
2013	34,303 (10.5)	18,694 (11.6)	12,377 (10.0)	2012 (9.8)	1220 (5.7)
2014	33,946 (10.4)	18,769 (11.6)	11,699 (9.5)	1963 (9.6)	1515 (7.1)
2015	37,621 (11.5)	19,144 (11.9)	13,072 (10.6)	2006 (9.8)	3399 (15.8)
2016	41,302 (12.6)	20,242 (12.5)	14,894 (12.1)	1773 (8.6)	4393 (20.5)
2017	46,518 (14.2)	21,688 (13.4)	17,284 (14.0)	1681 (8.2)	5865 (27.3)
2018	15,550 (4.8)	6814 (4.2)	5977 (4.9)	562 (2.7)	2197 (10.2)

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TABLE 5
Characteristics of the study population at the time of the first observed intrauterine device insertion, pooled and by research site *(continued)*

Variables	Pooled (N=326,658)	KPNC (n=161,442)	KPSC (n=123,214)	KPWA (n=20,526)	RI (n=21,476)
Duration of lookback period (mo)					
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

Data are presented as number (percentage), unless otherwise specified.

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

[a] At least 1 of the following: abortion, aspiration and curettage, dilation and curettage, excision or biopsy of the cervix or uterus, ablation, colposcopy and other cervical procedures, hysteroscopy procedure, laminaria procedure, laparoscopy, lysis adhesions, myomectomy, nerve procedure, or salpingectomy or oophorectomy.

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Strengths and limitations

Key advantages of the APEX-IUD study are the retrospective design that enabled 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 the system during their enrollment. Thus, risk estimates could be underestimated. The results of this study depend on the 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, women did not seek treatment, or if treatments were not documented in the EHR.

Conclusion

This study has a large, sociodemographically 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 United States. Relative to a prospective study, the retrospective design of the APEX-IUD study enabled a larger study population with a longer follow-up time and was 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 can provide informative risk estimates that can be used to inform clinical practice. Future results from this study can provide valuable information based on real-world evidence about risk factors for IUD perforation and expulsion for clinicians.

Highlights

- Study methods and cohort data of the APEX-IUD study are presented in this report.
- The Food and Drug Administration mandated the APEX-IUD study to evaluate IUD-related uterine perforation and IUD expulsion.
- Key risk factors are as follows: breastfeeding and postpartum timing at IUD insertion.
- Variables were identified through structured data and natural language processing of 326,658 women with ≥1 IUD insertion (median continuous enrollment, 7.5 years). ■

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A.A., A.K.F., R.L., and J.S. are employees of Bayer, the marketing authorization holder for 3 intrauterine device brands, among others, that were included in this study. The remaining authors report no conflict of interest.

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Supplemental Material

Appendix A: data sources

Four data sources with electronic health records (EHRs) were used for this study: Kaiser Permanente Northern California (KPNC), Kaiser Permanente Southern California (KPSC), Kaiser Permanente Washington (KPWA), and Regenstrief Institute (RI). Data in different files within each data source were linked by the patient's identification number. Descriptions of the healthcare system for each source of data follow.

Kaiser Permanente Northern California

The KPNC region in California extends from Santa Rosa and Sacramento in the north, to Modesto in the east, to San Jose and Fresno in the south and includes the entire San Francisco Bay Area. It covers 21 hospitals and 238 medical offices. KPNC covers approximately 4 million patients, representing half of the commercially insured patients and one-quarter of patients with Medicare in the area. The patient population represents the diversity of age, sex, and race and ethnicity in the regions served.

Data for KPNC are housed within a comprehensive EHR system that captures every patient encounter in every department, including hospital, emergency, ambulatory surgical, specialist, and generalist care encounters; clinic visits and telephone encounters; physiological measures; procedures; laboratory and radiology testing; and diagnoses. The comprehensive EHR system was fully implemented in 2009. Standardized research data sets—including enrollment, sociodemographics, pharmacy, encounters, diagnoses, procedures, vital signs, census, and laboratory results—are maintained for the purposes of research. Data are linked across all data sets via a unique medical record number. Infant records are maintained and can be linked to the mother's delivery record data.

In the validation study, continuous enrollment in KPNC was measured via enrollment files. Of all intrauterine device (IUD) insertions in this healthcare system, 67% (more than 100,000) were in women with at least 12 months of continuous enrollment before the date of insertion.

Kaiser Permanente Southern California

Kaiser Permanente Southern California is Kaiser Permanente's largest region, with 4.6 million members who broadly represent the diversity of age, sex, and race and ethnicity in the Southern California population. KPSC covers 15 hospitals and over 234 medical offices.

The KPSC EHR system was fully implemented in 2008 and integrates all aspects of care, including pharmacy and laboratory services, appointments, registration, and billing. Standardized research data sets are maintained similar to those in KPNC, including date and site of care, diagnosis codes, procedure codes, vaccinations, prescription medications and dispensing activities, vital signs, radiology, clinical reports, telephone encounters, laboratory and pathology results, and member demographics and enrollment information.

Each KPSC member is assigned a unique medical record number on joining the health plan. This number is retained for life, irrespective of leaving and rejoining the health plan. This unique number allows for the linkage across all data sets (both clinical and administrative). The prenatal data set includes data on live births, and infant records can be linked to the mother's data.

In the validation study, continuous enrollment in KPSC was measured via enrollment files. Of all IUD insertions in this healthcare system, 67% (more than 80,000) were in women with at least 12 months of continuous enrollment before the date of insertion.

Kaiser Permanente Washington

Based in state of Washington, KPWA (formerly the Group Health Cooperative, a nonprofit health system) currently serves approximately 700,000 members and provides primary, specialty, hospital, home health, and inpatient skilled nursing care on a prepaid (capitation) basis. Members in the healthcare system represent the diversity of age, sex, and race and ethnicity of the geographic region. About two-thirds of members receive comprehensive care at Kaiser Permanente medical facilities (Group Practice). KPWA has 36 care locations across the state plus 4 additional facilities with specialties, such as eye care and mental health, in addition to 24/7 urgent care centers. The remaining members receive care from contracted provider networks in geographic areas not served by KPWA medical facilities but reimbursed by KPWA.

The EHR system was fully implemented in 2006 and includes data sets on enrollment, encounters, diagnoses, procedures, vital signs, radiology, pathology, laboratory tests, and pharmacy dispensing. Data are linked across all data sets via a unique member identifier. The mother-infant data set includes data on women with live births and linked infant records.

In the validation study, continuous enrollment in KPWA was measured via enrollment files. Of all IUD insertions in this healthcare system, 64% (more than 15,000) were in women with at least 12 months of continuous enrollment before the date of insertion.

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The RI has research access to the Indiana Health Information Exchange, which represents over 16 million patients and includes clinical data from 117 Indiana hospitals, 38 core hospital systems, and the state and local public health departments of Indiana. Data from healthcare encounters were available for this study since 2001 and were captured in a standardized fashion. Data are linked via a unique identifier across institutions.

In the validation study, continuous enrollment was measured via healthcare encounters. Of all IUD insertions in this healthcare system, 74% (approximately 5700) were in women with at least 1 clinical encounter 12 months or more before the date of insertion.

Appendix B: evaluation of change from International Classification of Diseases, Ninth Revision, to International Classification of Diseases, Tenth Revision, Clinical Modification codes on outcomes

Algorithms for the outcome variables of uterine perforation and IUD expulsion were validated in these 4 data sources before use of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) coding. No formal validation of the algorithms with ICD-10-CM codes to identify uterine perforation or IUD expulsion was done in this study. However, the proportion of patients at risk who had 1 of these outcomes was evaluated before and after the implementation of ICD-10-CM coding to evaluate consistency over time.

In the pooled data (Supplemental Table), the proportion of women with a uterine perforation was 0.11% in the 12 months before ICD-10-CM code implementation and 0.12% in the 12 months after ICD-10-CM code implementation (which occurred on October 1, 2015). The proportion of women with an IUD expulsion in the 12 months before and 12 months after ICD-10-CM code implementation was 0.72% and 0.77%, respectively. At each research site, the proportions before and after ICD-10-CM code implementation were relatively consistent, with the exception of RI, where the estimates were based on a small number of events. The RI identified most cases from natural language processing (so there would be little impact of the ICD-9 or ICD-10-CM code changes), and they reviewed the records of all potential cases to verify case status.

Appendix C: propensity score modeling

For the final analyses, propensity scores are used to calculate weights for each IUD insertion within each risk factor group. The weights are "overlap weights."[1] This method has an advantage of not requiring trimming of observations; therefore, observations where there is significant overlap among groups are up-weighted, and observations where there is very little overlap are down-weighted, compared with regular inverse probability treatment weighting. To assess whether covariates are balanced across risk factor groups after weighting, the distribution of each variable is compared among categories of the risk factor variable, and balance parameters (ie, standardized differences) are calculated.[2] Pairwise balance parameters (ie, pairwise standardized differences) are used for the categorical risk factor variable (postpartum timing), in which each category is compared with the referent group. The balance among risk factor groups is assessed overall and within each site. If the groups are unbalanced on key covariates after application of overlap weighting, then the logistic regression model is revised by including interaction terms with the data source, and the covariate balance among the groups overall and within each data source is reevaluated on the basis of the revised model.[3,4] When satisfactory balance between the exposed and unexposed groups is achieved (in general, absolute standardized difference of <0.2), the weighting is incorporated in modeling for confounder-adjusted outcome assessments.

Supplemental References

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3. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc 1984;79:516–24.
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SUPPLEMENTAL TABLE

Proportion of patients with an IUD who had a uterine perforation or IUD expulsion within the 12 months before and 12 months after the implementation of ICD-10-CM coding

	12 mo before ICD-10 implementation			12 mo after ICD-10 implementation		
Site	Patients at risk, N	Uterine perforation, n (%)	IUD expulsion, n (%)	Patients, N	Uterine perforation, n (%)	IUD expulsion, n (%)
Pooled	84,929	93 (0.11)	614 (0.72)	91,851	108 (0.12)	709 (0.77)
KPNC	46,297	57 (0.12)	392 (0.85)	49,866	65 (0.13)	455 (0.91)
KPSC	31,116	20 (0.06)	168 (0.54)	32,668	29 (0.09)	191 (0.58)
KPWA	4442	6 (0.14)	35 (0.79)	4313	5 (0.12)	38 (0.88)
RI	3074	10 (0.33)	19 (0.62)	5004	9 (0.18)	25 (0.50)

ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; *IUD*, intrauterine device; *KPNC*, Kaiser Permanente Northern California; *KPSC*, Kaiser Permanente Southern California; *KPWA*, Kaiser Permanente Washington; *RI*, Regenstrief Institute.

Anthony et al. Association of uterine perforation and expulsion of intrauterine device study methods. Am J Obstet Gynecol 2021.