# Intrauterine device-related uterine perforation incidence and risk (APEX-IUD): a large multisite cohort study

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## Summary

**Background** Reports of perforation risk related to intrauterine devices (IUDs) inserted immediately post partum and among non-post-partum individuals are scarce, and previous studies with only 12-month follow-ups underestimate the risk. Breastfeeding at IUD insertion and insertion within 36 weeks post partum have been associated with increased risk of uterine perforation. The aim of these analyses was to compare the incidence and risks of IUD-related uterine perforations by non-post-partum and post-partum intervals at IUD insertion, and among post-partum individuals, to assess the impact of breastfeeding on these outcomes.

**Methods** We did a multisite cohort study in the USA, using electronic health records (EHR). Study sites were three health-care systems and a site that used data from a health-care information exchange. The study population included individuals who were aged 50 years or younger and had an IUD insertion between Jan 1, 2001, and April 30, 2018. Individuals were excluded if they had not been in the health-care system for at least 12 months before IUD insertion. The primary outcome for this analysis was any IUD-related uterine perforation diagnosis for the first IUD insertion in this time period. Both complete and partial IUD-related perforations were identified. Chart abstraction was done to validate EHR-based algorithms or confirm perforations. The crude rate and cumulative incidence of uterine perforation were evaluated by non-post-partum and post-partum intervals at IUD insertion in the full cohort, and by breastfeeding status in a subcohort of post-partum individuals. Cox models estimated crude and adjusted hazard ratios (aHRs).

**Findings** Data from 326 658 individuals in the full cohort and 94 817 individuals in the post-partum subcohort were analysed. In the full cohort, we identified 1008 uterine perforations (51·2% complete), with the 5-year cumulative incidence being the lowest in the non-post-partum group (0·29%, 95% CI 0·26–0·34). The aHR for the post-partum interval relative to non-post partum ranged from 2·73 (95% CI 1·33–5·63; 0 to 3 days post partum) to 6·71 (4·80–9·38; 4 days to ≤6 weeks post partum). The post-partum subcohort of individuals with breastfeeding information had 673 uterine perforations (62% complete), with a 5-year cumulative incidence of 1·37% (95% CI 1·24–1·52) and an increased risk with breastfeeding (aHR 1·37, 95% CI 1·12–1·66).

**Interpretation** Although the risk for uterine perforation with IUD insertion 4 days to 6 weeks or less post partum is nearly seven times that of insertion non-post partum, perforation remains an incredibly rare event for all clinical time points. Despite a slight increased risk of perforation with breastfeeding at IUD insertion, the benefits of breastfeeding and effective contraception generally outweigh risks and should have little clinical impact. Therefore, IUD insertion timing should be based on individual desire for IUD contraception and patient convenience to assure an IUD insertion can occur. Careful follow-up of individuals at higher risk of uterine perforation is warranted.

**Funding** Bayer AG.



## Introduction

Intrauterine devices (IUDs) are highly effective contraceptives that decrease unintended pregnancy rates, short-interval pregnancies, and abortions.[1] Worldwide, 14% of women use IUDs, with prevention of unintended pregnancy exceeding 99% in the first year of use.[2,3] Adverse events associated with IUD insertion occur rarely and include uterine perforation, estimated at a rate of 1·1–3·6 per 1000 insertions.[4-10] Uterine perforation might be recognised at the time of insertion or later with symptoms of abdominal pain and cramping, or in an asymptomatic individual long after the event when IUD strings are not visualised on speculum examination. Diagnosis at more than 1 year after insertion occurs in a large proportion of individuals and could happen at presentation for IUD removal.[6,9] If the perforation is through the uterine wall (complete), retrieval from the abdominal cavity requires surgery, either laparoscopy or laparotomy with general anaesthetic. If the IUD is embedded in the uterine wall but has not entered the abdominal cavity (partial), hysteroscopy might be necessary for removal.

It is important for individuals and providers to have information about the benefits and risks of IUD use to

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*Study group members are listed at the end of the paper

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## Research in context

### Evidence before this study

At study inception on March 1, 2018, with database searches (PubMed, Embase, Medline, Medmeme, Reactions Weekly, and EudraVigilance) in all languages using the terms "IUD," "intrauterine device," and "uterine perforation," one large relevant cohort study was identified: the European Active Surveillance Study on Intrauterine Devices (EURAS-IUD), a prospective study in six European countries. After study initiation, the literature was routinely monitored for additional published studies, until the last search on Dec 15, 2021. Smaller studies limited to a 12-month follow-up probably underestimated intrauterine device (IUD)-related uterine perforation and provided scarce data on partial versus complete perforations. Data on risks of IUD-related uterine perforation for insertions in non-post-partum individuals (nulliparous or beyond 52 weeks post partum) and those immediately post partum are scarce. EURAS-IUD reported that breastfeeding at IUD insertion (*vs* not breastfeeding) and insertion within 36 weeks post partum (*vs* more than 36 weeks) were associated with a small increased risk of uterine perforation.

### Added value of this study

This multisite US population-based cohort study (the Association of Perforation and EXpulsion of IntraUterine Devices) of 326 658 IUD insertions of devices currently on the market, identified 1008 uterine perforations (of which 51% were complete). Using data from electronic health records, we provide accurate estimates for a rare outcome. We showed that uterine perforations were least frequent among insertions in non-post-partum individuals. Insertions 0 to 3 days post partum or beyond 14 weeks had lower perforation risks than other post-partum intervals. Complete perforations were rare in non-post-partum individuals and not observed in IUD insertions 0 to 3 days post partum. Over half of IUD-related uterine perforations were recognised beyond 12 months from insertion among non-post-partum individuals (55%), whereas the majority among post-partum individuals were recognised within 12 months from insertion (63%). Among individuals 52 weeks or less post partum, we found an increased risk of uterine perforation with breastfeeding at IUD insertion, but this added risk was smaller than previously reported and was most pronounced in the later post partum insertions.

### Implications of all the available evidence

Optimal timing of IUD insertions should be informed by science and individuals' choices for pregnancy prevention. Non-post-partum individuals can be reassured by the low 5-year cumulative incidence of IUD-related uterine perforation of 0·29%. The low IUD-related uterine perforation risk for insertions 0 to 3 days post partum must be balanced with the known high risk of expulsion. The benefits of breastfeeding and effective contraception generally outweigh the slightly increased risk of uterine perforation observed with breastfeeding; the increased risk should have little meaningful clinical impact.

make informed choices; however, large, population-based studies providing precise and separate risk estimates for complete and partial uterine perforation incidence are scarce. Risk of uterine perforation in individuals with an IUD placed immediately post partum (after placenta removal) or in individuals who are beyond 1 year since delivery has not been well described. Further, risk estimates related to IUD insertions at different time intervals in the year following a delivery or while breastfeeding are limited. Early studies provided conflicting results, had small numbers, and often included devices no longer on the market.[4,5,11] The largest study—the European Active Surveillance Study on Intrauterine Devices (EURAS-IUD)—was a 12-month prospective observational study with a 5-year subcohort follow-up, done in six European countries with recruitment between 2006 and 2012.[6,7] EURAS-IUD found that breastfeeding at the time of IUD insertion (*vs* not breastfeeding) was associated with a five to six fold increased risk of uterine perforation. Evaluating only two post-partum intervals (≤36 weeks *vs* >36 weeks), the researchers observed a three-fold increase in uterine perforation risk among those who had insertion within 36 weeks post partum. The objective of these analyses was to compare the incidence and risks of IUD-related uterine perforations in post-partum individuals by post-partum interval and in individuals who were non-post partum (>52 weeks post partum or nulliparous) from the Association of Perforation and EXpulsion of IntraUterine Devices (APEX-IUD), a US multisite study of 326 658 individuals. Among post-partum individuals, we compared uterine perforation risk among those who were and were not breastfeeding at the time of IUD insertion. We present new data on partial versus complete perforations, more granular data on post-partum interval risks, and data on subpopulations previously not well described, including non-post-partum and immediate post-partum insertions.

## Methods

### Study design and participants

APEX-IUD was a US Food and Drug Administration mandated multisite cohort study using data from electronic health records (EHRs). The study was done within three health-care systems (Kaiser Permanente Northern California [KPNC], CA, USA; Kaiser Permanente Southern California [KPSC], CA, USA; and Kaiser Permanente Washington [KPWA], WA, USA) and a research site using data from a health-care information exchange (Regenstrief Institute [RI]; Indiana, USA). Study

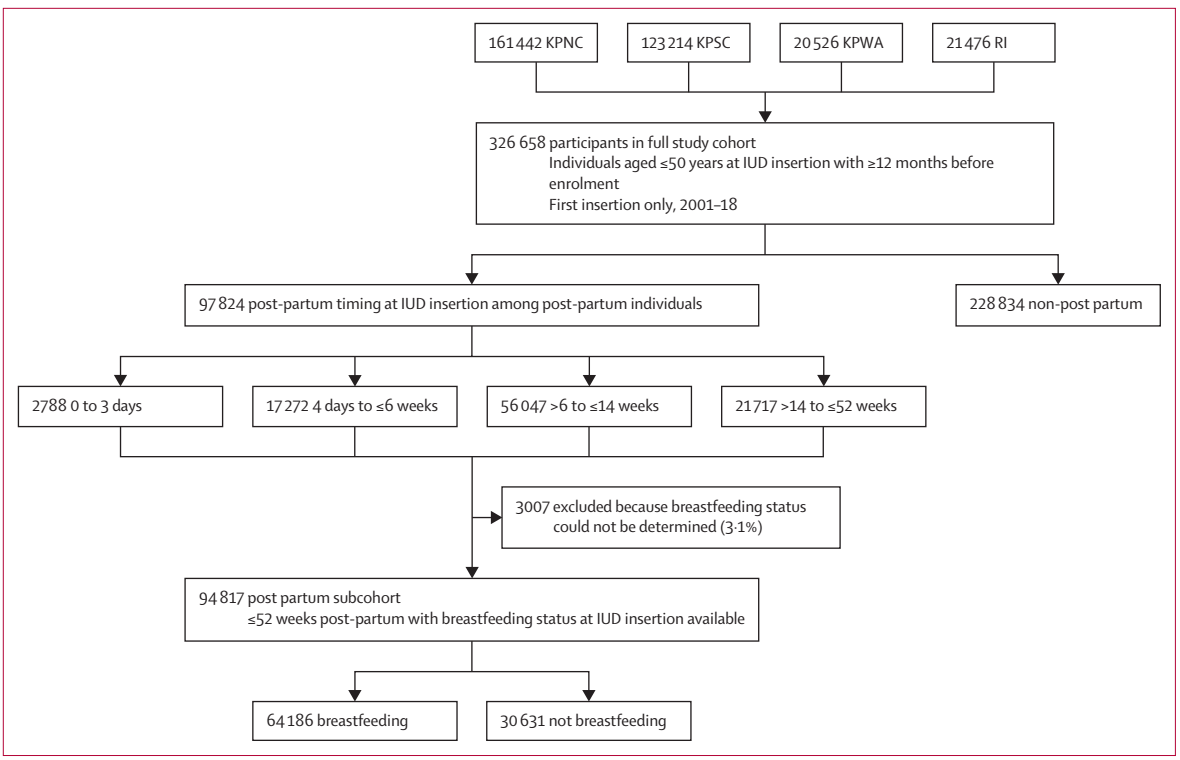


***Figure 1:*** **Full study cohort and post-partum subcohort**
Full cohort included non-post-partum individuals (greater than 52 weeks post partum or nulliparous individuals) and post-partum individuals (within 52 weeks from delivery). Post-partum subcohort included individuals within 52 weeks from delivery with known breastfeeding status. IUD=intrauterine device. KPNC=Kaiser Permanente Northern California. KPSC=Kaiser Permanente Southern California. KPWA=Kaiser Permanente Washington. RI=Regenstrief Institute.

methods, including power calculations, control for bias from confounding using propensity scores, and validation of outcomes and exposures, have been described in detail previously[12,13] and are summarised briefly in this section. All participating research sites received either institutional review board approval or exemption for the conduct of this study; KPSC also received approval from California State agencies for vital statistics data use.

The study population included individuals who were aged 50 years or younger at IUD insertion and in the health-care system for at least 12 months before IUD insertion. The earliest date for an individual to be included varied by research site, depending on when EHR data became available (Jan 1, 2001 for RI; Jan 1, 2007 for KPWA; Jan 1, 2009 for KPSC; and Jan 1, 2010 for KPNC), and the latest date was April 30, 2018, for all sites. If an individual had multiple IUD insertions, only the first insertion in the study period was included in the analyses. Individuals were followed up from the time of IUD insertion to uterine perforation or the earliest occurrence of one of the following: IUD expulsion, removal, reinsertion, or expiration; pregnancy, hysterectomy, or other sterilisation procedure; disenrolment from the health-care system (KP sites); last clinical encounter (RI); end of the study period, when all data collection stopped (June 30, 2018); or death. All individuals were included in the full cohort (n=326 658) and were either post partum (≤52 weeks of delivery) or non-post partum (>52 weeks post partum or nulliparous) at the time of IUD insertion. A subcohort (n=94 817) included post-partum individuals with information on breastfeeding status at IUD insertion (figure 1). The terms post partum, non-post partum, and breastfeeding herein refer to an individual's status at the time of IUD insertion.

## Procedures

Data from EHRs were in both structured and unstructured formats from patients' records and linked mother–infant records. Structured data included the International Classification of Diseases, Ninth Revision or Tenth Revision, Clinical Modification (ICD-9-CM or ICD-10-CM); Diagnostic and Procedural Codes; Medication Codes; Current Procedural Terminology Codes; and Healthcare Common Procedural Coding System Codes. Additionally, two sites (KPNC and KPSC) had structured data on breastfeeding status. Unstructured data consisted of clinical notes. Operational definitions were developed that included code lists for structured data and search terms to apply to unstructured data using natural language processing.[12] The definitions were agreed upon centrally and analytic datasets were created at each research site. Data were submitted to the data-coordinating centre in a standard format for analyses.

| | Full cohort (non-post-partum and post-partum interval; n=326 658)* | Post-partum subcohort (breastfeeding status; n=94 817)† |
|---|---|---|
| Person-years at risk | 641 427 | 182 738 |
| Breastfeeding status | | |
| Yes | 64 186 (19·6%) | 64 186 (67·7%) |
| Post-partum time of IUD insertion | | |
| 0 to 3 days | 2788 (0·9%) | 2647 (2·8%) |
| 4 days to ≤6 weeks | 17 272 (5·3%) | 16 933 (17·9%) |
| >6 to ≤14 weeks | 56 047 (17·2%) | 54 697 (57·7%) |
| >14 to ≤52 weeks | 21 717 (6·6%) | 20 540 (21·7%) |
| Non-post partum (>52 weeks post partum or nulliparous) | 228 834 (70·1%) | 0 |
| Age, years | 32·0 (8·3) | 29·3 (5·7) |
| Age category | | |
| ≤28 years | 119 469 (36·6%) | 40 360 (42·6%) |
| >28 to ≤36 years | 107 871 (33·0%) | 44 643 (47·1%) |
| >36 to ≤50 years | 99 318 (30·4%) | 9814 (10·4%) |
| Race or ethnicity‡ | | |
| Asian or Pacific Islander | 38 911 (11·9%) | 12 335 (13·0%) |
| Hispanic Black | 696 (0·2%) | 208 (0·2%) |
| Hispanic other | 56 180 (17·2%) | 15 066 (15·9%) |
| Hispanic White | 42 501 (13·0%) | 20 159 (21·3%) |
| Non-Hispanic Black | 28 323 (8·7%) | 7255 (7·7%) |
| Non-Hispanic White | 137 102 (42·0%) | 34 092 (36·0%) |
| Other or multiple | 16 357 (5·0%) | 4741 (5·0%) |
| Recent smoker§ | | |
| Yes | 32 623 (10·0%) | 7519 (7·9%) |
| BMI, kg/m² | 28·5 (6·99) | 28·7 (6·18) |
| BMI category¶ | | |
| Underweight | 3689 (1·1%) | 541 (0·6%) |
| Normal weight | 113 675 (34·8%) | 28 587 (30·1%) |
| Overweight | 96 81 (29·4%) | 32 628 (34·4%) |
| Obese | 107 674 (33·0%) | 32 883 (34·7%) |
| Dysmenorrhoea in the past year | | |
| Yes | 15 266 (4·7%) | 2249 (2·4%) |
| Menorrhagia in the past year | | |
| Yes | 32 552 (10·0%) | 898 (0·9%) |
| Uterine fibroids | | |
| Yes | 17 416 (5·3%) | 3617 (3·8%) |
| Parity‖ | | |
| ≤1 | 128 577 (39·4%) | 31 789 (33·5%) |
| >1 | 148 985 (45·6%) | 57 376 (60·5%) |
| Caesarean delivery any time before IUD insertion** | | |
| Yes | 54 295 (16·6%) | 25 792 (27·2%) |
| (Table 1 continues in next column) | | |

| | Full cohort (non-post-partum and post-partum interval; n=326 658)* | Post-partum subcohort (breastfeeding status; n=94 817)† |
|---|---|---|
| (Continued from previous column) | | |
| Caesarean delivery for most recent delivery before IUD insertion | | |
| Yes | 23 245 (7·1%) | 22 551 (23·8%) |
| IUD type†† | | |
| Levonorgestrel-releasing | 259 234 (79·4%) | 72 201 (76·1%) |
| Copper | 63 664 (19·5%) | 22 004 (23·2%) |
| Concomitant gynaecological procedure‡‡ | | |
| Yes | 26 234 (8·0%) | 1561 (1·6%) |
| Indicator of difficult insertion§§ | | |
| Yes | 29 777 (9·1%) | 2763 (2·9%) |
| Annualised number of IUD insertions performed by provider in previous year | 52·0 (73·70) | 49·5 (79·52) |
| Duration of look-back period, months¶¶ | 56·8 (42·3) | 48·2 (35·0) |
| Min, max | 12, 435 | 12, 391 |
| Duration of follow-up, years | | |
| Median | 1·4 | 1·4 |
| Min, max | 0·01, 0·3 | 0·01, 0·3 |

Data are n (%) or mean (SD), unless stated otherwise. Research site and year of IUD insertion were included as variables in the propensity score. BMI=body-mass index. IUD=intrauterine device. *Full cohort included non-post-partum individuals (over 52 weeks post partum or nulliparous) and post-partum individuals (within 52 weeks from delivery). †Post-partum subcohort included individuals within 52 weeks from delivery with known breastfeeding status. ‡Unknown or missing: full cohort 2%; post-partum cohort 1%. §Unknown or missing: full cohort 1·7%; post-partum cohort 0·3%. ¶Unknown or missing: full cohort 1·7%; post-partum cohort 0·2%. ‖Unknown or missing: full cohort 11·8%; post-partum cohort 0·0%. **Unknown or missing: full cohort 11·9%; post-partum cohort 0·0%. ††Unknown or missing: full cohort 1·1%; post-partum cohort 0·7%. ‡‡At least one of the following: abortion, aspiration and curettage, dilation and curettage, excision or biopsy of cervix or uterus, ablation, colposcopy and other cervical procedures, hysteroscopy procedure, hygroscopic cervical dilator insertion, laparoscopy, lysis adhesions, myomectomy, nerve procedure (eg, pudendal or paracervical nerve procedure; chemodenervation; laparoscopic procedure to the uterine, abdomen, peritoneum, or omentum; or spinal canal injection), or salpingectomy or oophorectomy. §§Including need for cervical dilation, ultrasound guidance, paracervical block, use of misoprostol, and clinician indicating difficulty. ¶¶Look-back period=time period of data available before IUD insertion.

***Table 1:*** **Characteristics of the study population at the time of IUD insertion**

The primary exposures were post-partum status by time from delivery, and breastfeeding status at IUD insertion. In the full cohort, post-partum status was defined relative to the most recent delivery and categorised as: 0 to 3 days post partum (immediate); 4 days to 6 weeks or less post partum; more than 6 weeks to 14 weeks or less post partum; more than 14 weeks to 52 weeks or less post partum; or non-post partum (>52 weeks post partum or nulliparous).

Among post-partum individuals, breastfeeding status was defined as: yes, if breastfeeding was documented within 30 days before IUD insertion or after insertion; no, if there was documentation that breastfeeding stopped before insertion or the most recent documentation of breastfeeding was more than 30 days before insertion; or unknown, never mentioned. Post-partum individuals with unknown breastfeeding status (n=3007, 3·1%) were excluded from the subcohort.

Covariates included research site, demographics, and risk factors at the time of IUD insertion based on all the available information since the earliest enrolment date (KP sites) or earliest clinical encounter (RI site; 12-month minimum pre-insertion). Risk factors included smoking status, body-mass index (BMI), reproductive and gynaecological factors (eg, parity or uterine fibroids), and information about the IUD insertion procedure (year, IUD type, indicators of difficult insertion, concomitant gynaecological procedure, or provider experience).[12]

### Outcomes

The primary outcome for this analysis was any IUD-related uterine perforation diagnosis, defined as complete (IUD in pelvis or abdomen), partial (IUD embedded in myometrium or cervical stroma), or undetermined. Chart abstraction was done to validate EHR-based algorithms or confirm perforations. An additional primary outcome, IUD expulsions, was reported separately.[14]

### Statistical analysis

Descriptive analyses for all variables of interest were done separately for the full cohort and the post-partum subcohort. Rates of uterine perforation were defined as the crude incidence rates reported as the number of outcomes per 1000 person-years at risk with exact 95% CIs.[15] Cumulative incidence was estimated using the Kaplan-Meier method (1 – Kaplan-Meier estimate). The full cohort was analysed by non-post-partum and post-partum intervals, and the post-partum subcohort by breastfeeding status.

Cox proportional hazards models were used to estimate crude hazard ratios (HRs) and adjusted HRs (aHRs) for any perforation. The proportional hazards assumption was met except for IUD insertions 0 to 3 days post partum, for which data were sparse. aHRs were estimated using propensity score overlap weighting.[16] A multinomial logistic regression model was used to calculate propensity scores for non-post-partum and post-partum intervals (full cohort) and binary logistic regression for breastfeeding status (post-partum subcohort). Additional details on overlap weighting and selection for confounders have been published previously[12] and are included in the appendix (pp 2–5).

Variables in both propensity score models included six demographic variables, eight clinical variables, and one provider-related variable; the breastfeeding propensity score model included an additional three clinical variables (appendix p 4). To achieve better balance between exposure categories within each site, product terms were included for age x site, smoker x site, IUD insertion year x site, and parity x site in the non-post-partum and post-partum interval model, and post-partum interval x site in the breastfeeding model. Within the post-partum subcohort, the product term between post-partum interval and breastfeeding status was included to estimate the combined effect of post-partum interval and breastfeeding status.

There were two post hoc analyses: incidence of complete and partial perforations; and a refinement of the post-partum timing exposure from a 4-category variable to a 5-category variable (splitting the ≤6 week category further to 0 to 3 days and 4 days to ≤6 weeks).

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

The study population comprised 326 658 individuals in the full cohort and 94 817 individuals in the post-partum subcohort, with mean ages of 32·0 (SD 8·3) years and 29·3 (5·7) years, respectively (table 1). In both cohorts, less than 45% of individuals were non-Hispanic White (full cohort, 137 102 [42·0%]; post-partum subcohort, 34 092 [36·0%]), and the mean BMI was 28·5 (SD 7·0) kg/m² in the full cohort and 28·7 (6·2) kg/m² in the post-partum subcohort. In the full cohort, most individuals (228 834 [70·1%]) were non-post partum; most post-partum insertions occurred within more than 6 weeks or 14 weeks and less (56 047 [17·2%]) and the fewest occurred within 0 to 3 days post partum (2788 [0·9%]). Most individuals had a levonorgestrel-releasing IUD (full cohort, 259 234 [79·4%]; post-partum subcohort 72 201 [76·1%]). Most insertions occurred between 2010 and 2018 (full cohort, 310 134 [94·9%]; post-partum subcohort 88 597 [93·4%]); median duration of follow-up after IUD insertion was 1·4 years for both the full cohort (IQR 0·5–3·0) and post-partum subcohort (0·6–2·9). The most common reasons for censoring were end of the study period, when all data collection stopped (32·0%); removal of IUD, replacement of IUD, or both (32·0%); and end of enrolment at KP sites or last clinical encounter at RI (25·6%). Details by research site are described elsewhere.[12]

There were 1008 uterine perforations in the full cohort, at a rate of 1·57 (95% CI 1·48–1·67) per 1000 person-years of follow-up (table 2); 57 perforations (5·7%) were diagnosed on the day of insertion and 215 (21·3%) were diagnosed within a month of insertion. There were no individuals with a perforation outcome who had pregnancy as a censoring event on the same date. The overall cumulative incidence of uterine perforation was 0·21% (95% CI 0·19–0·23) at 1 year and 0·61% (0·56–0·66) at 5 years (figure 2A). Non-post-partum individuals at IUD insertion had the lowest rate of perforation (0·68 per 1000 person-years, 95% CI 0·61–0·76) and the lowest cumulative incidence at 1 year (0·07%, 95% CI 0·06–0·08) and 5 years (0·29%, 0·26–0·34; table 2 and appendix p 6). Among post-partum individuals, insertions at 4 days to 6 weeks or less of delivery had the highest rate of perforation (5·53 per 1000 person-years, 95% CI 4·75–6·40; table 2) and the highest cumulative incidence at 1 year (0·78%,

See Online for appendix

| | Insertions | Person-years | Complete perforation | | Partial perforation | | Any perforation* | |
|---|---|---|---|---|---|---|---|---|
| | | | Events | Rate† | Events | Rate† | Events | Rate† |
| Full study cohort | 326 658 | 641 427 | 516 | 0·80 (0·74–0·88) | 488 | 0·76 (0·69–0·83) | 1008 | 1·57 (1·48–1·67) |
| Post-partum timing at IUD insertion | | | | | | | | |
| 0 to 3 days | 2788 | 4641 | 0 | 0·00 (0·00–0·79) | 11 | 2·37 (1·18–4·24) | 11 | 2·37 (1·18–4·24) |
| 4 days to ≤6 weeks | 17 272 | 32 533 | 98 | 3·01 (2·45–3·67) | 82 | 2·52 (2·00–3·13) | 180 | 5·53 (4·75–6·40) |
| >6 to ≤14 weeks | 56 047 | 110 574 | 280 | 2·53 (2·24–2·85) | 136 | 1·23 (1·03–1·45) | 417 | 3·77 (3·42–4·15) |
| >14 to ≤52 weeks | 21 717 | 40 676 | 59 | 1·45 (1·10–1·87) | 32 | 0·79 (0·54–1·11) | 91 | 2·24 (1·80–2·75) |
| Non-post partum (>52 weeks or no delivery) | 228 834 | 453 004 | 79 | 0·17 (0·14–0·22) | 227 | 0·50 (0·44–0·57) | 309 | 0·68 (0·61–0·76) |
| Post-partum cohort | 94 817 | 182 738 | 420 | 2·30 (2·08–2·53) | 253 | 1·38 (1·22–1·57) | 673 | 3·68 (3·41–3·97) |
| Breastfeeding status at IUD insertion | | | | | | | | |
| Yes | 64 186 | 123 903 | 340 | 2·74 (2·46–3·05) | 186 | 1·50 (1·29–1·73) | 526 | 4·25 (3·89–4·62) |
| No | 30 631 | 58 836 | 80 | 1·36 (1·08–1·69) | 67 | 1·14 (0·88–1·45) | 147 | 2·50 (2·11–2·94) |
| Breastfeeding at IUD insertion | | | | | | | | |
| 0 to 3 days | 2302 | 3517 | 0 | 0·00 (0·00–1·05) | 9 | 2·56 (1·17–4·86) | 9 | 2·56 (1·17–4·86) |
| 4 days to ≤6 weeks | 13 903 | 26 066 | 79 | 3·03 (2·40–3·78) | 64 | 2·46 (1·89–3·14) | 143 | 5·49 (4·62–6·46) |
| >6 to ≤14 weeks | 39 348 | 78 143 | 219 | 2·80 (2·44–3·20) | 100 | 1·28 (1·04–1·56) | 319 | 4·08 (3·65–4·56) |
| >14 to ≤52 weeks | 8633 | 16 176 | 42 | 2·60 (1·87–3·51) | 13 | 0·80 (0·43–1·37) | 55 | 3·40 (2·56–4·43) |
| Not breastfeeding at IUD insertion | | | | | | | | |
| 0 to 3 days | 345 | 791 | 0 | 0·00 (0·00–4·67) | 1 | 1·26 (0·03–7·05) | 1 | 1·26 (0·03–7·05) |
| 4 days to ≤6 weeks | 3030 | 5776 | 16 | 2·77 (1·58–4·50) | 17 | 2·94 (1·71–4·71) | 33 | 5·71 (3·93–8·02) |
| >6 to ≤14 weeks | 15 349 | 30 059 | 53 | 1·76 (1·32–2·31) | 34 | 1·13 (0·78–1·58) | 87 | 2·89 (2·32–3·57) |
| >14 to ≤52 weeks | 11 907 | 22 210 | 11 | 0·50 (0·25–0·89) | 15 | 0·68 (0·38–1·11) | 26 | 1·17 (0·76–1·72) |
| Non-post partum (>52 weeks or no delivery) | 228 834 | 453 004 | 79 | 0·17 (0·14–0·22) | 227 | 0·50 (0·44–0·57) | 309 | 0·68 (0·61–0·76) |

Data were n or rate (95% CI). In the full study cohort there were 1008 perforations; 516 (51·2%) were complete, 488 (48·4%) were partial, and four (0·4%) were undetermined. Among non-post-partum insertions, 79 (25·6%) of 309 perforations were complete. In the post-partum cohort there were 673 perforations; 420 (62·4%) were complete and 253 (37·6%) were partial. Among breastfeeding individuals at insertion, 340 (64·6%) of 526 perforations were complete. Perforations were defined as complete (IUD in pelvis or abdomen), partial (IUD embedded in myometrium or cervical stroma), or undetermined. IUD=intrauterine device. *Includes complete, partial, and undetermined. †Per 1000 person-years (95% CI).

*Table 2:* **Complete, partial, and undetermined perforations: number, crude incidence rate per 1000 person-years, and 95% CIs, stratified by post-partum timing of IUD insertion and breastfeeding status at IUD insertion**

0·65–0·93) and 5 years (1·98%, 1·61–2·43; figure 2A). Among IUD insertions at 0 to 3 days post partum, only one perforation was recognised in the first 6 months, and 1-year cumulative incidence was low (0·22%, 95% CI 0·08–0·60). The proportion of perforations diagnosed more than 12 months after IUD insertion was 42% overall and greater among non-post-partum insertions (55%) than post-partum insertions (37%).

The post-partum subcohort included 673 uterine perforations, at a rate of 3·68 (95% CI 3·41–3·97) per 1000 person-years of follow-up (table 2). Cumulative incidence was 0·52% (95% CI 0·47–0·57) at 1 year and 1·37% (1·24–1·52) at 5 years (figure 2B). Individuals who were breastfeeding at the time of IUD insertion had a higher perforation rate per 1000 person-years of follow-up (4·25, 95% CI 3·89–4·62) compared with non-breastfeeding individuals (2·50, 2·11–2·94; table 2 and appendix p 7). Cumulative incidence of perforation was almost double in breastfeeding individuals (1·61%, 95% CI 1·43–1·81) compared with non-breastfeeding individuals (0·88%, 0·71–1·08) at 5 years (figure 2B). Rates of uterine perforation were higher in earlier post-partum intervals (beginning at 4 days to ≤6 weeks post partum) compared with later intervals (appendix pp 8–9), regardless of breastfeeding status.

Of the 1008 perforations, 516 (51·2%) were complete, 488 (48·4%) were partial, and 4 (0·4%) were undetermined (table 2). Among non-post-partum insertions, 79 (25·6%) of 309 perforations were complete, with a rate of 0·17 (95% CI 0·14–0·22) per 1000 person-years (table 2 and appendix p 10), and cumulative incidences of 0·03% (95% CI 0·02–0·04) at 1 year and 0·05% (0·04–0·06) at 5 years (data not shown). Complete perforations occurred at the highest rate in individuals who were 4 days to 6 weeks or less post partum (98 [54·4%] of 180 individuals), at 3·01 per 1000 person-years (95% CI 2·45–3·67), and none were diagnosed in individuals with IUD insertion at 0 to 3 days post partum.

Of the 673 perforations in the post-partum subcohort, 420 (62·4%) were complete and 253 (37·6%) were partial (table 2 and appendix p 10). Among breastfeeding

individuals, complete perforations were proportionately greater than partial perforations (appendix p 10). As the post-partum interval increased, rates of complete perforation declined in non-breastfeeding individuals but remained stable in breastfeeding individuals.

Compared with non-post-partum insertions (reference group), all post-partum intervals were at an increased risk of uterine perforation; this ranged from an aHR of 2·73 (95% CI 1·33–5·63) for IUD insertions 0 to 3 days post partum to an aHR of 6·71 (4·80–9·38) for IUD insertions at 4 days to 6 weeks or less post partum (figure 3A). Among post-partum individuals, breastfeeding was associated with an increased risk of uterine perforation (crude HR 1·69, 95% CI 1·41–2·03; aHR 1·37, 95% CI 1·12–1·66; figure 3B).

## Discussion

This multisite US population-based study of 326 658 ethnically diverse individuals with IUD insertions in 2001–18 identified 1008 uterine perforations, of which approximately half were complete. The median follow-up was 1·4 years and 228 834 (70%) individuals were non-post partum (>52 weeks post partum or nulliparous). The 5-year cumulative incidence for perforation was low overall (0·61%), with the risk for non-post-partum individuals (0·29%) being roughly half that of the lowest post-partum group with insertions more than 14–52 weeks post partum (0·74%). Among post-partum individuals, perforation rates were highest in IUD insertions 4 days to 6 weeks or less post partum, with a 5-year cumulative incidence of 1·98%. Perforations in immediate post-partum insertions were rare; none were complete. The subcohort of 94 817 individuals within 52 weeks post partum experienced 673 perforations, and the risk of perforation was 37% higher in breastfeeding individuals (*vs* non-breastfeeding individuals).

Rates of uterine perforation reported in other studies[8,10] of at least 12 months' duration but with smaller numbers are, in general, lower than our overall estimates. Uterine perforations are often recognised at IUD removal, which could be as late as 12 years after insertion, depending on IUD type. Therefore, rate estimates from studies of 12 months and less tend to underestimate this rare outcome.[7,9] In APEX-IUD, 37% of perforations in post-partum insertions and 55% of perforations in non-post-partum insertions were recognised beyond 12 months from insertion. In the 5-year follow-up of EURAS-IUD, 39 009 insertions occurred, with 77 perforations overall: 59 perforations per 27 630 insertions for levonorgestrel-releasing IUDs at a rate of 2·1 per

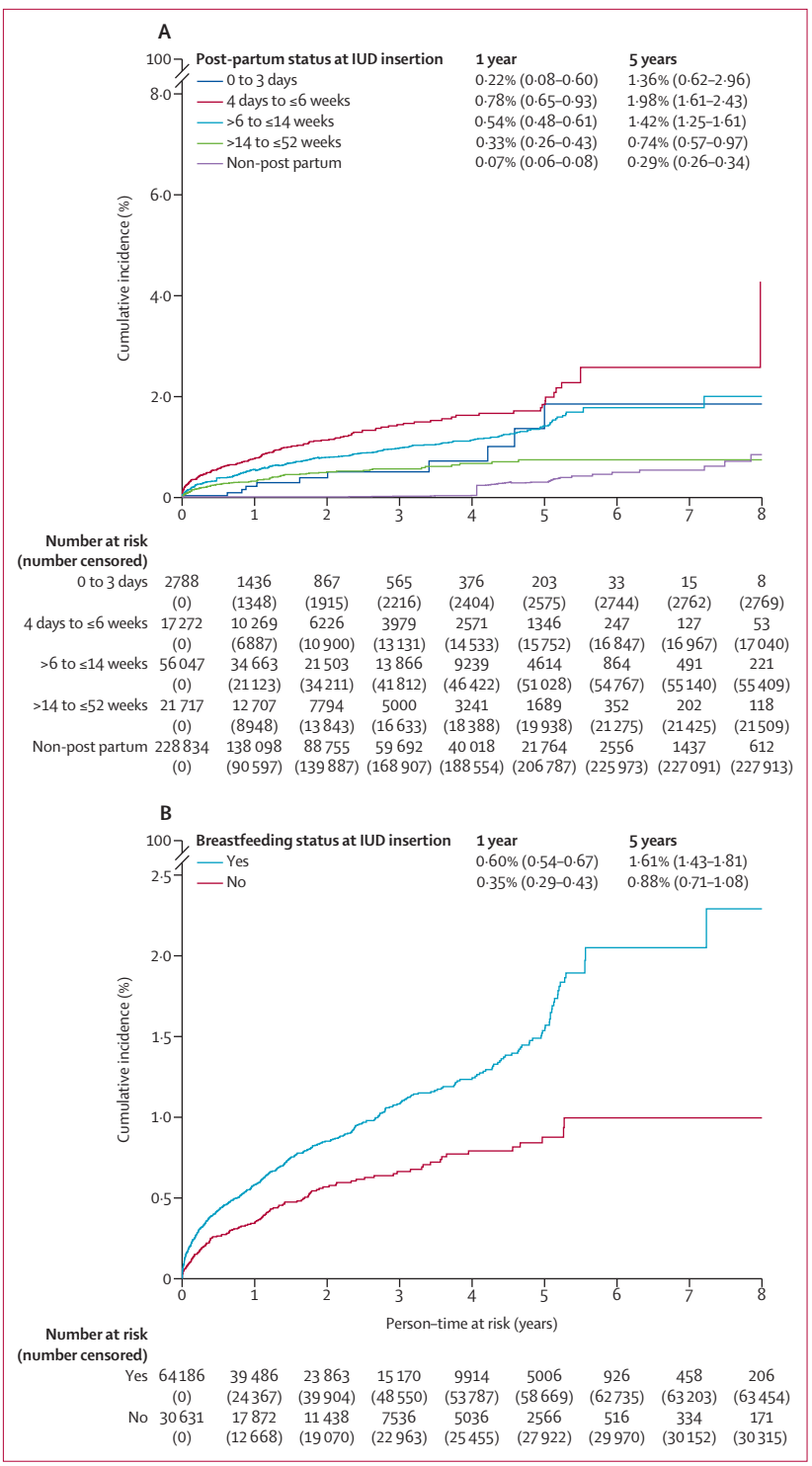


***Figure 2:*** **Cumulative incidence with 95% CIs of uterine perforation detection in (A) full cohort by non-post-partum and post-partum intervals at IUD insertion and (B) post-partum subcohort by breastfeeding status at IUD insertion**

Full cohort included non-post-partum individuals (>52 weeks post partum or nulliparous individuals) and post-partum individuals (within 52 weeks from delivery). Post-partum subcohort included individuals within 52 weeks from delivery with known breastfeeding status. Overall cumulative incidence of uterine perforation in the full cohort was 0·21% (95% CI 0·19–0·23) at 1 year and 0·61% (0·56–0·66) at 5 years. Overall cumulative incidence of uterine perforation in the post-partum cohort was 0·52% (0·47–0·57) at 1 year and 1·37% (1·24–1·52) at 5 years. IUD=intrauterine device.

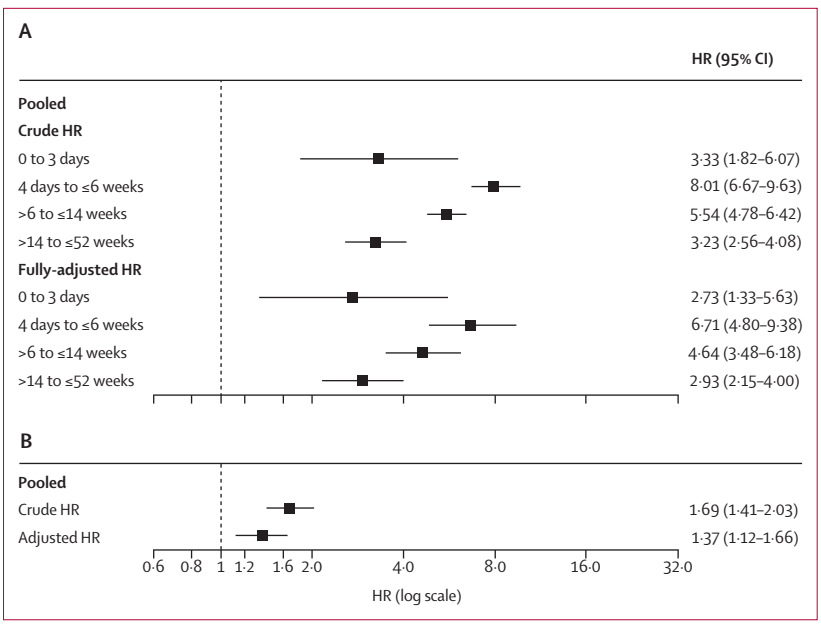


***Figure 3:*** **Crude and adjusted HRs of uterine perforation in (A) full cohort comparing post-partum interval IUD insertions to non-post-partum IUD insertions (reference group) and (B) post-partum subcohort comparing individuals breastfeeding at IUD insertion with individuals not breastfeeding (reference group)**
Full cohort included non-post-partum individuals (greater than 52 weeks post partum or nulliparous individuals) and post-partum individuals (within 52 weeks from delivery). Post-partum subcohort included individuals within 52 weeks from delivery with known breastfeeding status. In the full cohort, fully adjusted HRs were adjusted for breastfeeding and propensity score variables, including: IUD type; menorrhagia; age (tertiles); race or ethnicity; whether participant was a recent smoker; duration of look-back period (quartiles); calendar year of IUD insertion; body-mass index (categorical); dysmenorrhoea; uterine fibroids; parity; livebirth within past 52 weeks; most recent delivery; concomitant gynaecological procedure; difficult insertion; provider experience; site; and year of IUD insertion × site interactions. In the post-partum subcohort, propensity score variables included: post-partum interval; IUD type; menorrhagia; age (tertiles); race or ethnicity; whether participant was a recent smoker; duration of look-back period (quartiles); calendar year of IUD insertion; body-mass index (categorical); dysmenorrhoea, uterine fibroids; parity; caesarean before IUD insertion; caesarean ever; concomitant gynaecological procedures; difficult insertion; provider experience; livebirth before IUD insertion; site; and post-partum × site interaction. HR=hazard ratio. IUD=intrauterine device.

1000 insertions, and 18 perforations per 11 379 insertions for copper IUDs at a rate of 1·6 per 1000 insertions.[6] Although differences in study methodologies preclude direct comparison of perforation rates between EURAS-IUD and APEX-IUD, risk estimates from both studies were of a similar magnitude and in the same direction. Moreover, loss to follow-up makes long-term prospective studies challenging. For instance, in EURAS-IUD, data on IUD status were missing in more than a quarter of the population at the 5-year follow-up.[6] APEX-IUD refined the 36-week or less post-partum interval described by EURAS-IUD[6,7] and showed that the highest uterine perforation rates were among insertions 4 days to 6 weeks or less post partum. This is the timeframe that many post-partum IUDs are inserted in the USA.[17] Biologically, uterine involution occurs during this interval and involves tissue remodelling as the uterine size diminishes up to 8 weeks post partum,[18] but is individually variable, making it difficult for the provider to estimate the uterine size. Comparatively, immediate post-partum IUD insertion is done under direct visualisation at caesarean delivery or could be performed with or without ultrasound guidance at vaginal deliveries.[19] Uterine anatomy after vaginal delivery assures IUD insertion through a wide-open cervical canal but is also associated with a higher rate of expulsions and IUD malpositioning, probably due to a larger uterine cavity.[20,21] To our knowledge, there are no reliable estimates of uterine perforation rates for IUD insertion immediately post partum (0–3 days).[4,5] It is important to separate immediate post-partum insertions from other post-partum insertions previously associated with a higher risk for uterine perforation.[4–7]

We showed an increased risk of uterine perforation associated with breastfeeding individuals (*vs* non-breastfeeding individuals), as did the EURAS-IUD study.[7] Physiologically, breastfeeding individuals experience uterine contractions with milk let-down. They are in a low-oestrogen state similar to that of postmenopausal individuals, resulting in diminished myometrial collagen with fewer cross-links, myometrial thinning, and reduced pliability.[22–24]

Previous estimates of complete and partial uterine perforations tend to be limited by small numbers, short follow-up duration, report of IUDs no longer on the market,[4,5,11] or ungeneralisable populations. Roughly half of uterine perforations in our study were complete. This finding is important because clinical management varies by type of perforation (complete *vs* partial). Notably, a secondary analysis of 12-month follow-up data from EURAS-IUD revealed that, for insertions in the year post partum, 80% of perforations were complete, whereas for insertions beyond the post-partum year, 70% of perforations were complete.[25] In comparison, complete perforations were not diagnosed in IUD insertions at 0–3 days post partum in APEX-IUD, and complete perforations were rare in non-post-partum individuals. Rates of complete perforation were highest in individuals between 4 days to 6 weeks or less post partum, and among breastfeeding individuals, complete perforations were proportionately greater than partial perforations; this finding constitutes a cautionary message for providers inserting IUDs in this post-partum window and warrants further study.

The APEX-IUD study of ethnically diverse individuals in the USA, nearly ten times larger than any other study that evaluated IUDs currently on the market with more than 12 months of follow-up, adds precision to existing risk estimates for a rare outcome and provides previously unavailable risk estimates at discrete post-partum timing intervals. Because our cohort was large, at 5 years after IUD insertion, 29 616 individuals in the full cohort and 7572 in the post-partum subcohort were still being followed up. The methodology employed gives timely and accurate estimates with extensive adjustment for measured potential confounders through propensity score overlap weights, minimisation of misclassification by using all available look-back time, and coded plus free-text information previously validated by chart review to define variables.[12,13]

Limitations are acknowledged, including potential misclassification of the outcome and exposures and loss to follow-up. The dates of uterine perforation reflect the date of diagnosis, not necessarily the time of the perforation; nor were we able to track symptoms from insertion to diagnosis. The cumulative incidence of perforation based on Kaplan-Meier methods might be overestimated because IUD removal could be considered as a competing event (ie, precluding the occurrence of the outcome once the event has occurred).[26,27] However, this is unlikely to have biased the HR estimate because it is doubtful that IUD removal is related to exposure and risk of perforation. As evidenced by the cumulative incidence, some perforations were recognised at removal. Our median 1·4 years of follow-up might underestimate perforation rates if individuals are disenrolled from health-care systems before IUD removal, but 29 616 individuals in the full cohort and 7572 in the post-partum subcohort were still being followed up at 5 years. The rate of partial perforations might be overestimated, perhaps particularly so in the year post partum. The overestimation might result from an increase in health-care use, as well as increased surveillance stemming from the perceived potential for differential risk of perforation according to the timing of IUD insertion or presence of breastfeeding.[6,7] APEX-IUD combined insertions done on post-partum days 0–3, but more than 98% of these insertions were done on the day of delivery (day 0); immediate post-placental insertions (within 10 min of delivery) could not be identified. Misclassification of breastfeeding status was possible, since status was not necessarily collected at the time of IUD insertion; however, in 90·7% of individuals in the post-partum cohort, structured data were collected at frequent intervals. Breastfeeding status was recorded independently of outcome and was known in 97% of individuals. We recognise presumed heterogeneity in the breastfeeding exposure, particularly in the post-partum group of more than 14 days and 52 weeks or less.

Potential unmeasured confounding, sparse data in the 0 to 3 day post-partum group, missing data, and limitations of the HR are acknowledged. Missingness was low overall but was 12% for parity in the non-post-partum group. After weighting, the standardised difference between the four post-partum intervals and non-post-partum group was small (<0·20) for all key measured covariates except for the 0 to 3 day post-partum group, which was the smallest and differed in some characteristics (race or ethnicity, BMI, and provider experience). Any residual confounding due to unmeasured factors or missing data was likely non-differential. The HR was reported as a single average over the follow-up. Although the proportional hazards assumption was met except for IUD insertions 0–3 days post partum, the HR should be interpreted with caution because it might change over time simply due to changes in the pool of patient characteristics during the follow-up period (built-in selection bias), as more cases occur among those most susceptible.[28]

Providers should use tailored risk estimates while consenting for IUD insertion, considering nulliparity or distant delivery, post-partum timing, and breastfeeding. Nulliparous individuals and those beyond 52 weeks post partum at insertion can be reassured that the cumulative 5-year incidence of complete uterine perforation, requiring intra-abdominal surgical removal, is only 0·05% (95% CI 0·04–0·06). IUD perforations were highest among insertions 4 days to 6 weeks or less post partum; however, only 5·3% of the full cohort (17·9% of the post-partum subcohort) had IUD insertions in this time period and there were only 1089 IUD insertions 4 days to 4 weeks and less post partum (324 [29·8%] were at 4 weeks). With new recommendations from the American College of Obstetricians and Gynecologists and the US Centers for Disease Control and Prevention for early post-partum visits, there is potential opportunity for further study of IUD insertions done in the outpatient setting up to 6 weeks post partum. For individuals considering immediate post-partum IUD insertion, uterine perforation is rare, but must be considered in the context of known risk of expulsion of at least 10%[19] and potential need for immediate and effective contraception. The benefits of breastfeeding and effective contraception outweigh any slight increased risk of uterine perforation observed with breastfeeding, and perforation risks probably have little meaningful clinical impact on individual choices.

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**Contributors**

SDR advised on the design of the study and the analyses, interpreted the results, and drafted and critically revised the manuscript. XZ led the conduct of the analyses, interpreted the results, and critically revised the manuscript. LI advised on the design of the study and the analyses, oversaw data collection at KPWA, interpreted the results, and critically revised the manuscript. JLG advised on the design of the study and the analyses, oversaw data collection at RI, interpreted the results, and critically revised the manuscript. JFP, TR-B, MJF, DAP, MER, KJR, AA, FP, and JS advised on the design of the study and the analyses, interpreted the results, and critically revised the manuscript. MAA advised on the design of the study and the analyses, oversaw data collection at KPNC, interpreted the results, and critically revised the manuscript. DG advised on the design of the study and the analyses, oversaw data collection at KPSC, interpreted the results, and critically revised the manuscript. MM, ALA, GC, JMS, FX, VYC, TMI, and HST provided input on the analyses, interpreted the results, and critically revised the manuscript. CWS, SH, and JW contributed to the design of the study and conduct of the analyses, interpreted the results, and critically revised the

manuscript. MSA led the design of the study, oversaw the analyses, interpreted the results, and critically revised the manuscript.
The underlying study data were verified by XZ and JW. All authors made a substantial contribution to this work, gave final approval of the manuscript to be published, and agree to be accountable for the work. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

#### Declaration of interests

SDR received research funding from Bayer during the conduct of the study and has received royalties from UpToDate. LI received research funding from Bayer during the conduct of the study. XZ, KJR, CWS, SH, JW, and MSA are employees and MER was an employee of RTI-HS, which received research funding from Bayer during the conduct of the study. DG, MJF, JMS, FX, VYC, TMI, and HST are employees of KPSC, which received research funding from Bayer during conduct of the study. JLG is an employee of RI, which received research funding from Bayer during the conduct of the study. JFP has received research funding from CooperSurgical, Bayer Healthcare Pharmaceutical, and Merck & Co. MAA, MM, ALA, and GC are employees of and TR-B and DAP were employees of KPNC, which received research funding from Bayer during the conduct of the study. AA, FP, and JS are employees of Bayer, the marketing authorisation holder for three IUD brands, among others, that were included in this study.

#### Data sharing

Data reported in this study are aggregated from electronic health records, which are not publicly shared. Individuals wishing to access disaggregated data, including data reported in this study, should submit requests for access to the corresponding author where the request will be reviewed by all coauthors for approval. De-identified data (including, as applicable, participant data and relevant data dictionaries) might be shared upon approval of analysis proposals with signed data-use access agreements in place.

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