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Title: Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUDInsertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)

Test Compound Number(s):
BAY86-5028, Mirena -
OS

Trade Name:

Mirena

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Performing Laboratory:
United States

Observational Study Information

Title	Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUD Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)
Version identifier of the final study report	Version 1.0
Date of last version of the final study report	3 March 2020
EU PAS Register number	33461
Active substance	Intrauterine contraceptives: plastic IUD with progestogen (ATC code G02BA03) and plastic IUD with copper (ATC code G02BA02)
Product	Mirena®, Skyla®, Liletta®, Kyleena®, and ParaGard® intrauterine devices
Product reference	
Procedure number	Not Applicable
Marketing authorization holder(s)	Bayer AG
Joint PASS	No

Research question and objectives	The overall goal of this study was to assess the impact of breastfeeding and timing of postpartum IUD insertion on uterine perforation and IUD expulsion (evaluated separately) in a representative population of US women. The study also evaluated risk of these outcomes in women with a recent (in the 12 months before IUD insertion) diagnosis of menorrhagia versus no recent diagnosis and by IUD type (copper versus LNG-releasing). Incidence rates and cumulative incidence of these events among the different exposure groups were calculated. An assessment of statistical interaction between postpartum timing and breastfeeding at IUD insertion with uterine perforation was done. Other statistical interactions were evaluated for IUD type with breastfeeding or postpartum timing for both uterine perforation and IUD expulsion.
Country(-ies) of study	United States
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Marketing authorization holder(s)

Marketing authorization holder(s)	BAYER AG
MAH contact person	PPD

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1. Abstract

Title

Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUD Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)

Version 1.0

Keywords

Intrauterine device, postpartum, breastfeeding, menorrhagia, cohort study, IUD expulsion, uterine perforation

Rationale and background

Mirena, a levonorgestrel (LNG)-releasing intrauterine system (LNG-IUD), was approved by the United States (US) Food and Drug Administration (FDA) for use in the US in December 2000. In August 2015, FDA communicated to Bayer a new postmarketing requirement to conduct a study of incidence and risk factors for uterine perforation related to breastfeeding and timing of postpartum intrauterine device (IUD) insertion in US women. The concerns described by the FDA related to results from the European Active Surveillance Study for Intrauterine Devices (EURAS-IUD), which found an increased risk of uterine perforation with breastfeeding at the time of IUD insertion and with IUD insertions within 36 weeks of delivery in the studied European population.

Research question and objectives

The overall goal of this study was to assess the impact of breastfeeding and timing of postpartum IUD insertion on uterine perforation and IUD expulsion (evaluated separately) in a representative population of US women. The study also evaluated risk of these outcomes in women with a recent diagnosis of menorrhagia (i.e., within the 12 months before the IUD insertion) versus no recent diagnosis and by IUD type (copper versus LNG- releasing). Incidence rates and cumulative incidence of these events among the different exposure groups were calculated. An assessment of statistical interaction between postpartum timing of IUD insertion and breastfeeding at the time of IUD insertion for uterine perforation was done. Other statistical interactions were evaluated for IUD type with breastfeeding at the time of IUD insertion or postpartum timing of IUD insertion for both uterine perforation and IUD expulsion.

Study design

The study was a retrospective cohort study set within four health care system data sources with electronic health records.

Setting

This study was conducted using data from three health care systems with electronic health records (Kaiser Permanente Northern California [KPNC], Kaiser Permanente Southern California [KPSC], Kaiser Permanente Washington [KPWA]) and one research institute with access to a health

information exchange, Regenstrief Institute (RI). The investigators at these sites (research partners) worked collaboratively to develop a common approach to study design and implementation.

Subjects and study size, including dropouts

The study included 326,658 women with at least one IUD insertion identified during the study period. The number of women included from each site differed (KPNC, 161,442; KPSC, 123,214; KPWA, 20,526; and RI, 21,476).

Variables and data sources

Variables included baseline characteristics such as demographic characteristics, clinical characteristics, procedure-related characteristics, indicators of a difficult IUD insertion, year of IUD insertion, data source, and provider-related characteristics. The exposures included postpartum timing of IUD insertion (using different time categories), breastfeeding status (yes or no) at the time of IUD insertion, type of IUD inserted (copper vs. LNG-releasing), and recent diagnosis of menorrhagia. The outcomes were uterine perforation and IUD expulsion. Continuous enrollment time was also measured. This information came from medical records that included both structured data (e.g., ICD [*International Classification of Diseases*] diagnosis and procedure codes, medication codes, and Common Procedural Terminology codes) and unstructured data (e.g., clinical notes).

Results

The crude incidence of uterine perforation ranged from 2.2 to 5.5 per 1,000 person-years for different categories of time of postpartum IUD placement among women who were ≤ 52 weeks postpartum and was 0.68 per 1,000 person-years for women who were > 52 weeks postpartum or had no recorded delivery in the last year. The risk (based on adjusted hazard ratios) of uterine perforation was approximately 190% to 570% higher among women with earlier postpartum IUD insertions (4 days to ≤ 6 weeks, 6 to ≤ 14 weeks, 14 to ≤ 52 weeks) than among those with IUD insertions > 52 weeks postpartum or with no recorded delivery in the previous 12 months (main comparator group). Among women with an IUD insertion within 3 days of delivery, the risk of uterine perforation was 170% higher than for women with insertions > 52 weeks postpartum or with no recorded delivery in the previous 12 months. The crude incidence of uterine perforation in women who were breastfeeding at the time of IUD insertion and within 52 weeks postpartum was 4.2 per 1,000 person-years and was 2.5 per 1,000 person-years for women who were not breastfeeding and within 52 weeks postpartum at the time of IUD insertion. Women who were breastfeeding at the time of IUD insertion and within 52 weeks postpartum were at a 40% higher risk of uterine perforation than women who were not breastfeeding and within 52 weeks postpartum.

The crude incidence of IUD expulsion ranged from 9.3 to 46.5 per 1,000 person-years in different categories of time of postpartum IUD placement among women who were ≤ 52 weeks postpartum and was 14.9 per 1,000 person-years for women who were > 52 weeks postpartum or had no recorded delivery in the last year. The risk of IUD expulsion (based on adjusted hazard ratios) was 20% higher in women with IUD insertions 4 days to 6 weeks postpartum and 40% higher in women with IUD insertions 14 to ≤ 52 weeks postpartum than in women with IUD insertions more than 52 weeks postpartum or with no recorded delivery. Among women with an IUD insertion within 3 days of delivery, risk of IUD expulsion was 430% higher than in those with an IUD insertion > 52 weeks postpartum or with no recorded delivery. The crude incidence of IUD expulsion was

10.2 per 1,000 person-years in women who were breastfeeding and within 52 weeks postpartum at the time of IUD insertion and 14.6 per 1,000 person-years for women who were not breastfeeding and were within 52 weeks postpartum at the time of IUD insertion. Women who were breastfeeding at the time of IUD insertion and within 52 weeks postpartum had a 30% lower risk of IUD expulsion than those who were not breastfeeding and were within 52 weeks postpartum at IUD insertion.

The crude incidence rates of uterine perforation were 1.6 per 1,000 person-years for women with LNG-IUDs and 1.3 per 1,000 person-years for women with copper IUDs. For IUD expulsion, the crude incidence rates were 14.0 per 1,000 person-years for women with LNG-IUDs and 14.1 per 1,000 person-years for women with copper IUDs. Women with LNG-IUDs were at a 50% higher risk of uterine perforation and 30% lower risk of IUD expulsion than women with copper IUDs.

Among women without a recorded delivery in the previous 52 weeks, the crude incidence rates of uterine perforation were 1.0 per 1,000 person-years in women with a recent diagnosis of menorrhagia (i.e., in the previous 12 months) and 0.6 per 1,000 person-years in those without a recent diagnosis. For IUD expulsion, the crude incidence rates were 40.0 per 1,000 person-years in women with a recent diagnosis of menorrhagia and 10.9 per 1,000 person-years in women without a recent diagnosis in the population of women without a recorded delivery in the previous 52 weeks. In this same population, the risk of uterine perforation was 50% higher and risk of IUD expulsion was about 180% higher in women with a diagnosis of menorrhagia in the previous 12 months than in women without such a diagnosis.

Discussion

Overall incidence of IUD-associated uterine perforation was low (ranging from 0.6 to 5.5 per 1,000 person-years depending on the exposure [e.g., menorrhagia, postpartum timing of IUD insertion] and category of the exposure [e.g., no recent menorrhagia diagnosis, 4 days to 6 weeks postpartum]). In this study population, uterine perforation risk appeared to be greatest for women with IUDs placed from 4 days to 6 weeks postpartum. Clinicians should be aware of this risk, and consideration should be given to delaying IUD insertion to a later postpartum time period. The results also suggest that IUD insertions done within the first 3 days after delivery are less likely to result in a uterine perforation than those done in later postpartum time periods (e.g., 4 days to 14 weeks postpartum) which also has clinical implications for optimal timing of insertions. Breastfeeding at the time of IUD insertion and a diagnosis of menorrhagia within the 12 months before IUD placement were also associated with higher risk of uterine perforation. LNG-IUDs also appeared to be associated with higher risk of uterine perforation than copper IUDs, but since Mirena, the most commonly used LNG-IUD, is indicated for women with menorrhagia, there is the potential for some residual confounding that should be further explored.

Overall, incidence of IUD expulsion (9 to 47 per 1,000 person-years, depending on the exposure and category of the exposure) was about 10-fold higher than incidence of uterine perforation. If unrecognized, complete IUD expulsion could result in unplanned pregnancy. IUD expulsions were most frequent with immediate postpartum placement (within 3 days postpartum), and these women should have follow-up in the postpartum period to assess expulsion. IUD expulsion was also higher among women with a diagnosis of menorrhagia within the previous 12 months, and counseling should be tailored to this population. Breastfeeding at the time of IUD insertion among those less than 52 weeks postpartum was associated with a lower risk of IUD expulsion. Compared with copper IUDs, LNG-releasing IUDs were also related to a lower risk of expulsion. The present study

might have overestimated risks related to partial IUD expulsions, as our definition of partial IUD expulsion was intentionally rather conservative and included malpositioned IUDs that were recognized on ultrasound and were replaced by the clinician.

Overall, in APEX IUD, the risk of uterine perforation was highest in women with IUD insertion 4 days to 6 weeks postpartum and among women who were ≤ 52 weeks postpartum and breastfeeding at the time of IUD insertion. The risk of IUD expulsion was highest in women with IUD insertion 0 to 3 days postpartum and among women with a recent diagnosis of menorrhagia. Clinicians should be aware of the higher risks of uterine perforation associated with IUD insertion during specific postpartum time periods and while women are breastfeeding and the higher risks of IUD expulsion with menorrhagia and immediate postpartum timing of IUD insertion and consider these factors while counseling their patients about IUD use.

Marketing Authorization Holder(s)

Bayer AG

Names and affiliations of principal investigators

See Section 3 below.

2. List of abbreviations

ATC	Anatomical Therapeutic Chemical (Classification System)
BF adjusted	fully adjusted for propensity scores and breastfeeding status
BMI	Body Mass Index
CI	Confidence Interval
DOR	Division of Research (KPNC)
EHR	Electronic Health Record
EMA	European Medicines Agency
EU	European Union
EU PAS Register	European Union Electronic Register of Post-Authorization Studies
EURAS-IUD	European Active Surveillance Study for Intrauterine Devices
FDA	Food and Drug Administration (United States)
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
ICD-10	*International Classification of Diseases, 10th Revision*
ICD-10-CM	*International Classification of Diseases, 10th Revision, Clinical Modification*
ID	Identification
IRB	Institutional Review Board
IRD	Incidence Rate Difference
IRR	Incidence Rate Ratio
ISPE	International Society for Pharmacoepidemiology
IT	Information Technology
IUD	Intrauterine Device
KPs	Kaiser Permanente data sources
KPNC	Kaiser Permanente Northern California
KPSC	Kaiser Permanente Southern California
KPWA	Kaiser Permanente Washington
LNG	Levonorgestrel
LNG-IUD	Levonorgestrel-Releasing Intrauterine System
MAH	Marketing Authorization Holder

NE	not estimable
NLP	natural language processing
PMR	Postmarketing Requirement
RDW	Research Data Warehouse (KPSC site)
RI	Regenstrief Institute
RR	Relative Risk
RTI-HS	RTI Health Solutions, a unit of RTI International, a nonprofit research organization
SD	Standard Deviation
US	United States
VDW	Virtual Data Warehouse (Kaiser Permanente sites)

3. Investigators

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4. Other responsible parties

None.

5. Milestones

Table 1: Milestones

Milestone	Planned date	Actual date	Comments
Protocol submitted to the FDA	December 2017	December 2017	
Updated (final) protocol submitted to the FDA		July 2018	Incorporated FDA's April 2018 comments
Statistical analysis plan submitted to the FDA		July 2018	
Study start	March 2018	September 2018	Date of agreement on protocol with FDA
Updated (final) statistical analysis plan submitted to the FDA		November 2018	Incorporated FDA's September 2018 comments
Study end (analyses completed)	December 2018	November 2019	See note
Final report of study results	December 2019	March 2020	See note

FDA = United States Food and Drug Administration.
Note: Actual milestone dates agreed with FDA.

6. Rationale and background

Mirena, a levonorgestrel (LNG)-releasing intrauterine system (hereafter, LNG-IUD), was approved for use in the United States (US) in December 2000 [1]. In August 2015, Bayer received a postmarketing requirement (PMR) from the US Food and Drug Administration (FDA) to conduct a study of incidence and risk factors for uterine perforation related to breastfeeding and timing of postpartum insertion in US women. The concerns described by the FDA related, in part, to results from the European Active Surveillance Study for Intrauterine Devices (EURAS-IUD).

EURAS-IUD was a 12-month prospective observational study in six European countries with recruitment between 2006 and 2012 [2]. Two cohorts were included, new users of LNG-releasing IUDs (n = 43,078) and new users of copper IUDs (n = 18,370).* During the 12 months of follow-up, there were 61 uterine perforations in the LNG-IUD group (1.4 per 1,000 insertions; 95% confidence interval [CI]: 1.1, 1.8) and 20 in the copper IUD group (1.1 per 1,000 insertions; 95% CI: 0.7, 1.7).

* Note: In this report, the term "IUD" is used to refer to both LNG-releasing intrauterine systems and copper intrauterine devices.

The authors concluded that breastfeeding at the time of IUD insertion was associated with a 6-fold increase in relative risk (RR) of uterine perforation for both groups (RR, 6.1; 95% CI: 3.9, 9.6), and there was no difference between the cohorts in this elevated risk associated with breastfeeding: LNG-IUD (RR, 6.3; 95% CI: 3.8, 10.5) and copper IUD (RR, 7.8; 95% CI: 2.8, 21.4). There was also an increased risk of uterine perforation among those who had the IUD inserted within 36 weeks after the most recent delivery (Table 2).

Table 2: Perforation incidence and relative risk stratified by breastfeeding status and time since last delivery

Time since last delivery	Incidence[a] of perforation (95% CI)		Relative risk (95% CI) of perforation if breastfeeding
	Breastfeeding		
	Yes	No	
≤ 36 weeks	5.6 (3.9, 7.9)	1.7 (0.8, 3.1)	**3.3 (1.6, 6.7)**
> 36 weeks	1.6 (0.0, 9.1)	0.7 (0.5, 1.1)	**2.2 (0.3, 16.3)**
Relative risk (95% CI) of perforation if last delivery ≤ 36 weeks ago	**3.4 (0.5, 24.8)**	**2.3 (1.1, 4.7)**	

CI = confidence interval.
[a] Incidence per 1,000 insertions.
Source: Heinemann et al. [2].

Uterine perforation risk was higher for patients of clinicians who inserted fewer than 50 IUDs per year. However, there was no association between uterine perforation and other potential confounding variables, including cervical dilation for IUD insertion, use of anesthesia for IUD insertion, and prior cesarean delivery [2].

In the US, compared with European Union (EU) countries, it is more common to place IUDs immediately postpartum; therefore, the FDA is particularly interested in understanding the risk of uterine perforation in relation to the duration of time from delivery to IUD placement. Because of the results of EURAS-IUD, the FDA was also interested to understand whether, in the context of US breastfeeding practices, there is an association between breastfeeding status at the time of IUD insertion and higher risk of uterine perforation.

In agreement with the FDA, a validation/feasibility study was conducted to support the proposed retrospective study approach for the Mirena IUD uterine perforation safety assessment PMR study in health care systems with electronic health records (EHRs). The validation/feasibility study was conducted in three health care systems with access to EHRs (Kaiser Permanente Northern California [KPNC], Kaiser Permanente Southern California [KPSC], Kaiser Permanente Washington [KPWA]) and a health care information exchange with EHRs (Regenstrief Institute [RI]). During the validation/feasibility study, algorithms were developed and validated to identify uterine perforation and IUD expulsion, and the feasibility of ascertaining data for breastfeeding status was reviewed. In addition, available data on difficulty of IUD insertion and continuous enrollment were assessed. In brief, the study demonstrated that it was feasible to identify breastfeeding status at the time of IUD insertion in these four health care system data sources, that women were enrolled in these health plans long enough to ascertain the outcomes of interest, that factors that might be indicative of a difficult IUD insertion could be identified, and that these validated algorithms could be used to identify uterine perforation and IUD expulsion [3]. The positive predictive values of the algorithms to identify uterine perforation were 77% (95% CI: 68%, 85%) for KPNC, 81% (95% CI: 72%, 88%) for KPSC, 82% (95% CI: 63%, 94%) for KPWA, and 47% (95% CI: 29%, 65%) for RI. The positive predictive values of the algorithms to identify IUD expulsion were 77% (95% CI:

68%, 85%) for KPNC, 87% (95% CI: 79%, 93%) for KPSC, 68% (95% CI: 58%, 77%) for KPWA, and 37% (95% CI: 28%, 46%) for RI. On the basis of these results, RI decided that they would review all identified possible uterine perforations and IUD expulsions for the PMR study. The FDA agreed that the results of the validation/feasibility study for these four data sources contained sufficiently reliable exposure and outcome information to address the PMR. The findings of the validation study have been published in a peer-reviewed journal [3].

The study described within this report is the retrospective PMR study assessing outcomes of uterine perforation and IUD expulsion in association with breastfeeding and postpartum exposures in the health care system/health information exchange data sources with EHRs, as requested by the FDA and conducted in accordance with the protocol accepted by FDA in September 2018 (version 2.0, dated 29 June 2018) and the statistical analysis plan (version 2.0, dated 24 October 2018), provided as stand-alone documents (see list in Annex 1). This report details the study design and methodology and provides estimates of the incidence and risk factors of uterine perforation among women using IUDs, as well as the effects of breastfeeding at the time of IUD insertion, the timing of IUD insertion postpartum, menorrhagia, and IUD type on the risk of uterine perforation and IUD expulsion.

During the time frame for this study, four brands of LNG-releasing IUDs were approved for use in the US:

- Mirena (approved by the FDA in December 2000 for use up to 5 years before removal or replacement) [1],
- Liletta (approved by the FDA in February 2015 for use up to 3 years before removal or replacement [4]; in October 2018, the approved duration of use was extended to 5 years [5], and in October 2019 Liletta was approved by the FDA for use up to 6 years [6]),
- Skyla (approved by the FDA in January 2013 for use up to 3 years) [7], and
- Kyleena (approved by the FDA in September 2016 for use up to 5 years) [8].

A copper IUD, ParaGard, has been available in the US since 1984 [9]; in 1994, it was approved for use up to 10 years [10]. All IUDs in use during the study time frame were included in the PMR study.

7. Research question and objective

The overall goal of this study was to assess the impact of breastfeeding and timing of postpartum IUD insertion on uterine perforation and IUD expulsion (evaluated separately) in a representative population of US women.

The study quantified the difference in risk of perforation and expulsion in (1) women who were breastfeeding at the time of IUD insertion versus women who were not breastfeeding at the time of IUD insertion and (2) women who had IUD insertion within different postpartum time periods (i.e., ≤ 6 weeks, > 6 weeks and ≤ 14 weeks, > 14 weeks and ≤ 52 weeks) versus women who had IUD insertion with no recorded delivery in the past 52 weeks. In addition, the study assessed the extent to which breastfeeding modifies the difference in risk of perforation and expulsion associated with the time period of postpartum IUD insertion. The study also assessed whether the risks of uterine perforation and/or IUD expulsion differed by the type of IUD (LNG-releasing vs. copper IUD) or by a diagnosis of menorrhagia in the year before IUD insertion, and whether there were

interactions of breastfeeding status and postpartum timing of IUD insertion with IUD type. The study estimated the prevalence of indicators of difficult insertion.

For all primary analyses, only the first IUD insertion observed in the study period was included in order to maintain independence of observations. Multiple insertions were considered only for objectives 18 and 26 (see Section 7.2). The objectives listed below were numbered sequentially to enable referencing of specific objectives within the analysis section.

7.1 Primary objective(s)

The primary objectives in this study were as follows:

1. To evaluate whether the risk of uterine perforation among women with an IUD inserted within 52 weeks of delivery who were breastfeeding at the time of first observed IUD insertion differed from the risk of uterine perforation among women with an IUD inserted within 52 weeks of delivery who were not breastfeeding at the time of first observed IUD insertion
2. To evaluate whether the risk of uterine perforation among women who had a first observed IUD insertion within different time periods postpartum (i.e., ≤ 6 weeks, > 6 weeks and ≤ 14 weeks, > 14 weeks and ≤ 52 weeks) differed from the risk of uterine perforation among women who had their first observed IUD insertion more than 52 weeks postpartum or had no recorded delivery within the past 52 weeks (including nulliparous women)
    - An additional analysis involved 5-level postpartum timing (i.e., 0 to 3 days, 4 days to ≤ 6 weeks, > 6 weeks to ≤ 14 weeks, > 14 weeks to ≤ 52 weeks) versus the > 52-week postpartum group

Both primary objectives evaluated a modification by the data source (i.e., interaction terms) to determine whether there was a significant interaction between data source and breastfeeding (objective 1) or timing of postpartum insertion (objective 2). Interaction terms for data source were included only for the objective(s) with statistically significant interaction(s).

7.2 Secondary objective(s)

There were descriptive and comparative secondary objectives in this study. The secondary objectives were grouped by type of analysis (i.e., rates, comparative, interaction) and outcome (i.e., uterine perforation, IUD expulsion, indicators of difficult insertion). Additional analyses were done that included two additional postpartum time cut points and the evaluation of risk of uterine perforation and IUD expulsion for women with menorrhagia for those who were more than 52 weeks postpartum (or with no recorded delivery). These additional analyses are included within the list of objectives below, but labeled as additional analyses.

Rates: uterine perforation

3. To estimate the incidence rate and cumulative incidence of uterine perforation among women using IUDs

4. To estimate the incidence rate and cumulative incidence of uterine perforation among women using IUDs for the following categories:
    - 0–3 days postpartum (cut point for additional analysis)
    - 4 days to ≤ 6 weeks postpartum (cut point for additional analysis)
    - ≤ 6 weeks postpartum
    - > 6 weeks and ≤ 14 weeks postpartum
    - > 14 weeks and ≤ 52 weeks postpartum
    - > 52 weeks postpartum, including women without recorded delivery within the past 52 weeks
    - ≤ 14 weeks postpartum
    - > 14 weeks postpartum, including women without recorded delivery within the past 52 weeks
    - ≤ 36 weeks postpartum
    - > 36 weeks postpartum, including women without recorded delivery within the past 52 weeks
5. To estimate the incidence rate and cumulative incidence of uterine perforation among women, within 52 weeks postpartum, who were and were not breastfeeding at the time of IUD insertion
6. To estimate the incidence rate and cumulative incidence of uterine perforation among women with different types of IUD (i.e., LNG-IUD and copper IUD)
7. To estimate the incidence rate and cumulative incidence of uterine perforation among women with and without menorrhagia in the 12 months before IUD insertion in the complete study population (and among those with no delivery in the previous 12 months [additional analysis])

Rates: IUD expulsion

8. To estimate the incidence rate and cumulative incidence of IUD expulsion among users of IUDs
9. To estimate the incidence rate and cumulative incidence of IUD expulsion among users of IUDs for the following categories:
    - 0–3 days postpartum (cut point for additional analysis)
    - 4 days to ≤ 6 weeks postpartum (cut point for additional analysis)
    - ≤ 6 weeks postpartum
    - > 6 weeks and ≤ 14 weeks postpartum
    - > 14 weeks and ≤ 52 weeks postpartum
    - > 52 weeks postpartum, including women without recorded delivery within the past 52 weeks

- ≤ 14 weeks postpartum
- > 14 weeks postpartum, including women without recorded delivery within the past 52 weeks
- ≤ 36 weeks postpartum
- > 36 weeks postpartum, including women without recorded delivery within the past 52 weeks

10. To estimate the incidence rate and cumulative incidence of IUD expulsion among women, within 52 weeks postpartum, who were and were not breastfeeding at the time of IUD insertion
11. To estimate the incidence rate and cumulative incidence of IUD expulsion among women with different types of IUD (i.e., LNG-IUD and copper IUD)
12. To estimate the incidence rate and cumulative incidence of IUD expulsion among women with and without menorrhagia in the 12 months before IUD insertion in the complete study population (and among those with no delivery in the previous 12 months [additional analysis])

Prevalence of difficult IUD insertion

13. To describe the prevalence of indicators of a difficult IUD insertion (e.g., need for cervical dilation, ultrasound guidance, paracervical block, use of misoprostol, clinician indicating difficulty) among all users

Comparative: uterine perforation

14. To estimate the adjusted hazard ratio (HR) of uterine perforation among women who had a first observed IUD insertion early in the postpartum period (i.e., up to 14 weeks postpartum) versus those who had a first observed IUD insertion late in the postpartum period (i.e., more than 14 weeks postpartum, including women without recorded delivery within the past 52 weeks)
15. To estimate the adjusted HR of uterine perforation among women who had a first observed IUD insertion ≤ 36 weeks postpartum versus women who had a first observed IUD insertion > 36 weeks postpartum, including women without recorded delivery within the past 52 weeks (this objective was performed as a sensitivity analysis; same cut point as in EURAS-IUD)
16. To estimate the adjusted HR of uterine perforation for women whose first observed IUD was a copper IUD versus women whose first observed IUD was an LNG-releasing IUD
17. To estimate the adjusted incidence rate ratio (IRR) and incidence rate difference (IRD) of uterine perforation at 1 year and 5 years of follow-up among women who had a first observed IUD insertion ≤ 36 weeks postpartum versus women who had a first observed IUD insertion > 36 weeks postpartum, including women without recorded delivery within the past 52 weeks (same analytic approach as EURAS-IUD)
18. To estimate the adjusted HRs of uterine perforation described in objectives 1, 2, and 14-16 across all subsequent insertions (i.e., not the first insertion) observed within the data. (The site-specific analyses were performed only if there were more than 20,000 subsequent IUD

insertions for that site. The pooled analysis included all sites regardless of the number of subsequent IUD insertions at a site.)

19. To estimate the adjusted HR of uterine perforation for women using an IUD who had at least one diagnosis code indicating menorrhagia in the 12 months before IUD insertion versus IUD users who did not have this indication in the complete study population (and among those with no delivery in the previous 12 months [additional analysis])

Comparative: IUD expulsion

20. To estimate the adjusted HR of IUD expulsion among women, within 52 weeks postpartum, who were breastfeeding at the time of first observed IUD insertion versus those who were not breastfeeding at the time of first observed IUD insertion
21. To estimate the adjusted HR of IUD expulsion for women who had a first observed IUD insertion early in the postpartum period (i.e., up to 14 weeks postpartum) versus those who had a first observed IUD insertion late in the postpartum period (i.e., more than 14 weeks postpartum, including women without recorded delivery within the past 52 weeks)
22. To estimate the adjusted HR of IUD expulsion for women who had a first observed IUD insertion ≤ 36 weeks postpartum versus women who had a first observed IUD insertion > 36 weeks postpartum, including women without recorded delivery in the past 52 weeks
23. To estimate the adjusted HRs of IUD expulsion for women who had a first observed IUD insertion in early postpartum categories versus women who had a first observed IUD insertion late in the postpartum period, using the following strata:
    - ≤ 6 weeks postpartum
    - > 6 weeks and ≤ 14 weeks postpartum
    - > 14 weeks and ≤ 52 weeks postpartum
    - > 52 weeks postpartum, including women without recorded delivery in the past 52 weeks (referent category)
    - An additional analysis involved 5-level postpartum timing (i.e., 0 to 3 days, 4 days to ≤ 6 weeks, > 6 weeks to ≤ 14 weeks, > 14 weeks to ≤ 52 weeks and the > 52 week postpartum [referent] groups)
24. To estimate the adjusted HR for IUD expulsion for women whose first observed IUD was an LNG-releasing IUD versus women whose first observed IUD was a copper IUD
25. To estimate the adjusted IRR, and IRD of IUD expulsion at 1 year and 5 years of follow-up among women who had a first observed IUD insertion ≤ 36 weeks postpartum versus women who had a first observed IUD insertion > 36 weeks postpartum, including women without a recorded delivery within the past 52 weeks
26. To estimate the adjusted HRs of IUD expulsion described in objectives 20-24 across all subsequent insertions (i.e., not the first insertion) observed within the data. (The site-specific analyses were performed only if there were more than 20,000 subsequent IUD insertions for that site. The pooled analysis included all sites regardless of the number of subsequent IUD insertions at a site.)
27. To estimate the adjusted HR of IUD expulsion for women using an IUD who had at least one diagnosis code indicating menorrhagia in the 12 months before IUD insertion versus IUD

users who did not have this indication in the complete study population (and among those with no delivery in the previous 12 months [additional analysis])

Interactions (effect modification)

28. To evaluate the extent to which breastfeeding status (yes vs. no) modified the association of uterine perforation for women with IUD insertion at different time periods postpartum (i.e., IUD insertion ≤ 14 weeks versus IUD insertion > 14 weeks postpartum) among women with a recorded delivery within the past 52 weeks at the time of the first observed IUD insertion
29. To evaluate the extent to which type of IUD (LNG-IUD vs. copper IUD) modified the association between uterine perforation and breastfeeding among women who were and were not breastfeeding at the time of first observed IUD insertion
30. To evaluate the extent to which type of IUD (LNG-IUD vs. copper IUD) modified the association between IUD expulsion and breastfeeding among women who were and were not breastfeeding at the time of first observed IUD insertion
31. To evaluate the extent to which type of IUD (LNG-IUD vs. copper IUD) modified the association between uterine perforation and postpartum timing of IUD insertion for women with IUD insertion at different time periods postpartum (i.e., ≤ 6 weeks, > 6 and ≤ 14 weeks, > 14 and ≤ 52 weeks) versus IUD insertion more than 52 weeks postpartum, including no recorded delivery within the past 52 weeks, at the time of the first observed IUD insertion
32. To evaluate the extent to which type of IUD (LNG-IUD vs. copper IUD) modified the association between IUD expulsion and postpartum timing of IUD insertion for women with IUD insertion at different time periods postpartum (i.e., ≤ 6 weeks, > 6 and ≤ 14 weeks, > 14 and ≤ 52 weeks) versus IUD insertion more than 52 weeks postpartum, including no recorded delivery within the past 52 weeks, at the time of the first observed IUD insertion

8. Amendments and updates

None after the start of data collection.

9. Research methods

9.1 Study design

A retrospective cohort study design was used to evaluate uterine perforation and IUD expulsion among women with an IUD insertion identified within EHR data. The study considered the impact of breastfeeding status at the time of IUD insertion and timing of IUD insertion during the postpartum period on the outcomes of uterine perforation and IUD expulsion.

This study included all women with evidence of an IUD insertion that had at least 12 months of enrollment history preceding IUD insertion. (RI, which does not have enrollment dates, required a clinical visit at least 12 months before IUD insertion.) The requirement of 12 months of enrollment before inclusion of IUD insertions was used to gather baseline data, including data on the exposures, timing of postpartum IUD placement, and breastfeeding.

Baseline data such as patient demographics, patient characteristics (e.g., personal history of gynecologic conditions such as endometriosis and fibroids), procedure characteristics, and

medications were collected from all available time before the index date (defined as the day of IUD insertion).

Patients were followed from the time of IUD insertion until the first occurrence of any of the following: IUD-related uterine perforation, IUD expulsion, IUD removal, indication of IUD reinsertion, indication of pregnancy, hysterectomy or other sterilization procedure, death, expiration of IUD (e.g., 5 years for Mirena), disenrollment from the health care system, or end of the study period. All person-time at risk that met these criteria was included, and there were no requirements for minimum or maximum follow-up time. All IUD insertions occurring with at least 12 months of enrollment before the IUD insertion that were noted within the data sources were included in the study. The index date was captured for each insertion, and baseline data were collected for each index date. The main analyses for the study assessed only the first observed IUD insertion for each woman during the study period. Secondary analyses were conducted assessing all subsequent IUD insertions (i.e., after the first observed IUD insertion). The sequential number of each insertion, as captured in the data for each woman, was collected and included as a baseline covariate within these secondary analyses.

9.2 Setting

This study was conducted using data from three health care systems with EHRs (KPNC, KPSC, and KPWA) and one research institute with access to a health information exchange, RI. The investigators at these sites (research partners) worked collaboratively to develop a common approach to study design and implementation as outlined in the following sections and detailed within the statistical analysis plan.

The exposure and outcome algorithms (operational definitions and natural language processing [NLP]) at all sites were developed collaboratively to capture the same concepts but differed where appropriate (e.g., some ICD codes performed better at some sites than at others due to variation in local coding practices, and NLP terms varied by site due to geographic differences in preferred medical terminology). Site investigators affiliated with each data system were responsible for implementation of the study protocol at their sites. Results are summarized in this final study report by RTI Health Solutions (RTI-HS) in collaboration with the site investigators and Bayer AG.

9.2.1 Study time frame

Time windows

The earliest possible start date for a woman to be eligible for the study participation was 01 January 2001 (after approval of Mirena in the US), and the latest date for a woman to be included in the study was 30 April 2018, 2 months before the end date of the data cut (30 June 2018). The study start date at each site was dictated by when EHRs were fully implemented or the time when Mirena was launched. Further, the start date at each site for inclusion in the breastfeeding assessment was dictated by the date at which breastfeeding data became available. The end date was chosen to coincide with the expected availability of complete data at the time of the data cut for the analysis. The start and end dates at each site are shown in Figure 1.

Index date

The index date was the date of an IUD insertion.

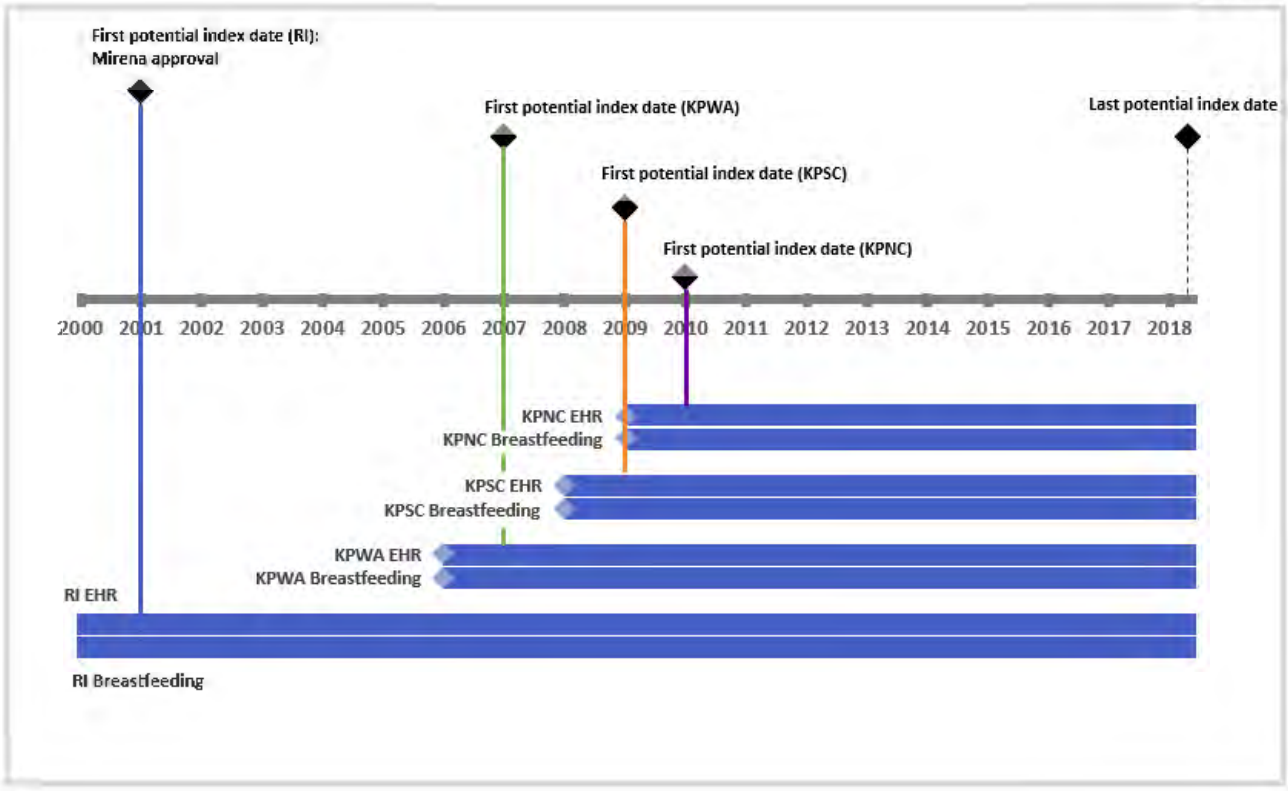


Figure 1: Start and end dates of electronic health record data and breastfeeding data, including first and last potential index dates, by data source

EHR = electronic health records; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute.
Note: RI EHRs were implemented prior to1990; data from 01 January 1990 were included in the period before the index date.

9.2.2 Selection criteria

Inclusion criteria for the source population

Each IUD insertion for each woman was eligible for inclusion in the study if it met *all* of the following criteria:

- Evidence in the data source of insertion of an IUD (LNG-releasing, copper, or unidentified type) during the study time window for each site (through 30 April 2018).
- Patient enrolled in the health care system or health information exchange with EHRs available for review for at least 12 months before the IUD insertion to ensure identification of any deliveries in the 12 months before IUD insertion and to provide a minimum time for capture of baseline data among IUD users.

Exclusion criterion for the source population

IUD insertions were excluded from the study if a patient met the following criterion *at the time of the IUD insertion*:

- Aged more than 50 years at the time of the IUD insertion (there was no lower age limit)

9.2.3 Study population

Source

This study was conducted using EHR data from four sites: KPNC, KPSC, KPWA, and RI.

Sampling strategy

The first observed IUD insertion for each woman that met study inclusion/exclusion criteria was included in the primary analyses. All subsequent IUD insertions occurring during the study period were included in the study for secondary analyses.

Study population characteristics/representativeness

The source population included women in the US. Three of the data sources included individuals with health maintenance organization insurance coverage on the west coast of the US (Washington state [including northern Idaho] and northern and southern California) and were ethnically diverse. The fourth data source was a health information exchange located in the midwest (Indiana), which included all patients regardless of health insurance status and had a larger proportion of African Americans than the other sites but a lower proportion of other minorities. The use of EHRs was implemented in each health care system at different times (Figure 1).

9.3 Subjects

The source population consists of members of KPNC, KPSC, and KPWA (formerly Group Health Cooperative) and patients who receive care from facilities enrolled in the Indiana Health Information Exchange (RI). The study population consisted of women with evidence in their EHR, of insertion of an LNG-releasing IUD, a copper IUD, or an unidentified type of IUD during the study period and who were aged ≤ 50 years at the time of the IUD insertion. Only those with EHR data available for review beginning 12 months before the day of IUD insertion were included in this study.

9.4 Variables

9.4.1 Baseline characteristics

Baseline characteristics were assessed before the index date for each eligible IUD insertion. The look-back period, all available data before the index date (unless otherwise specified for a particular variable), was used to evaluate patient characteristics and the potential for confounding. Because all patients in the study were required to have at least 12 months of data before the first index date, a minimum of 12 months of data from which to evaluate baseline characteristics were available (Figure 2). For some patients, more information was available, and all information within the data source was considered in order to reduce misclassification of baseline information [11].

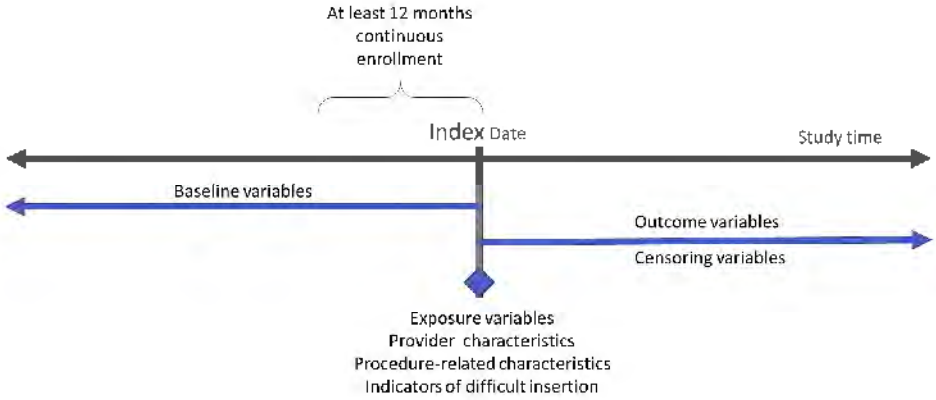


Figure 2: Covariate data collection around the index date

Demographic characteristics

The following demographic variables were assessed as potential confounders.

- *Age:* age in years as of the index date
  - Three categories divided at tertiles (or closest integer cut point [i.e., in years]) for descriptive tables
  - Continuous variable in propensity score models, if appropriate
- *Race/ethnicity:* categorical variable with nine categories: non-Hispanic white, Hispanic white, non-Hispanic black, Hispanic black, other Hispanic, Asian/Pacific Islander, multiple races/ethnicities, other race/ethnicity, unknown
- *Smoking status:* indicator variable, 0 = no recent smoking, 1 = recent smoking (active smoker within 365 days before index date)
- *Calendar year of the index date:* year of IUD insertion
- *Month of the index date (only KPNC and KPWA provided this information to RTI-HS):* 12-level categorical variable corresponding to month of the IUD insertion
- *Duration of the look-back period at the index date:* continuous variable with a minimum of 365 days; categorized (1 to ≤ 2 years, > 2 to ≤ 4 years, > 4 to ≤ 6.5 years, > 6.5 years)

Clinical characteristics

- *Body mass index (BMI), weight in kg divided by height in meters squared (kg/m^2):* continuous variable assessed at the index date or the closest date before or after the index date
  - If BMI was not recorded within the EHR, then weight and height closest to the index date (before or after the index date) was used to calculate BMI
- *Dysmenorrhea:* four-level categorical variable for whether the patient was diagnosed with dysmenorrhea and when relative to the index date
  - Diagnosed in the year before the index date, but not diagnosed before that time
  - Not diagnosed in the year before the index date, but was diagnosed before that time

- Diagnosis recorded both within year before the index date and before that time
- No diagnosis of dysmenorrhea within data

- *Fibroids:* indicator variable for whether the patient was ever diagnosed with uterine fibroids before the index date (0 = No, 1 = Yes)
- *Parity:* cumulative number of viable pregnancies (i.e., carried to at least 20 weeks gestation) before the index date

The following baseline characteristics were captured only among women who had at least one delivery before the index date:

- *Cesarean delivery* was captured in two variables:
  - Indicator variable for whether the patient ever had a cesarean delivery before the index date (0 = No, 1 = Yes)
  - Indicator variable for whether the patient had a cesarean delivery for the most recent delivery that is within 52 weeks before the index date (0 = No, 1 = Yes)

Procedure-related characteristics

- *Concomitant gynecological procedure:* indicator variable for whether the IUD insertion was performed during the same visit as another gynecological procedure or surgery (0 = No, 1 = Yes)
  - Concomitant gynecological procedures were categorized as either "abortion-related" (abortion, aspiration and curettage, dilation and curettage, laminaria) or "other" (excision/biopsy of cervix or uterus, ablation, colposcopy, hysteroscopy, laparoscopy, lysis adhesions, myomectomy, nerve procedure, salpingectomy/oophorectomy). If insufficient data were available to assess (RI only), then concomitant gynecological procedure was assigned as missing.
- *IUD insertion count:* count of the number of IUD insertions for this woman, including the current insertion, that was identified before or on the index date within the data source
- *Initial IUD insertion:* indicator variable for first insertion seen within data (0 = No, 1 = Yes)

Indicators of a difficult IUD insertion

- *Difficult insertion:* indicator variable for whether any of the following occurred on the index date (or in the 7 days before the index date for misoprostol): *cervical dilation, ultrasound guidance*, *paracervical block*, *provider note indicating difficult insertion*, *use of misoprostol* (0 = No, 1 = Yes).
- *Cervical dilation* was identified on the day of the IUD insertion and was classified as yes or no. If there was no information in the record that cervical dilation was done, then the classification was "no."
- *Ultrasound guidance* for the placement of the IUD was identified on the day of the IUD insertion and was classified as yes or no. If there was no information in the record that ultrasound was used to assess IUD uterine position, then the classification was "no."

- *Paracervical block:* indicator variable for whether the patient received a paracervical block during the IUD insertion procedure (0 = No, 1 = Yes). If there was no information in the record that a paracervical block was used, then the classification was "no."
- *Provider note indicating a difficult insertion or complicated procedure:* indicator variable for whether the patient record included a notation from the provider regarding a difficult insertion or complicated procedure (0 = No, 1 = Yes). If there was no notation of this in the record, then the classification was "no."
- *Use of misoprostol:* indicator variable for whether the patient received a misoprostol prescription in the 7 days before the IUD insertion procedure or took misoprostol for the procedure (0 = No, 1 = Yes).

Provider-related characteristics, where available (i.e., KPNC, KPSC, KPWA)

- *Provider number of IUD insertions in the previous year:* number of IUD insertions the provider performed in the previous year
- *Provider annualized number of IUD insertions in the previous year:* provider number of IUD insertions in previous year divided by the number of months provider was employed by health care system represented in data source
- *Categorical indicator for number of IUD insertions in the previous year:* 0 = fewer than 50 IUD insertions in the previous year, 1 = 50 or more IUD insertions in the previous year
- *Provider length of employment in the previous year:* continuous variable of the number of days employed within the health care system in the previous year (This variable was used to calculate provider annualized number of IUD insertions in the previous year.)

9.4.2 Exposure

- *Pregnancy delivery date:* the date on which delivery occurred.
- *Number of days postpartum* was calculated as the difference between the IUD insertion date and the date of the most recent delivery expressed in days. Data for days postpartum were not captured for women with no evidence of delivery in the 52 weeks before the index date.
- *Postpartum status* consisted of three variables: two dichotomous variables and a four-level categorical variable. In all of these variables, women with no evidence of delivery in the past year (52 weeks) were classified as "no delivery in the past 52 weeks."
    - *Postpartum status at IUD insertion for sensitivity analysis:* a dichotomous comparison of ≤ 14 weeks postpartum versus > 14 weeks postpartum (including women with no evidence of delivery in the previous 52 weeks)
    - *Postpartum status similar to EURAS-IUD:* a dichotomous comparison of IUD insertions occurring ≤ 36 weeks postpartum versus > 36 weeks postpartum (including women with no evidence of delivery in the previous 52 weeks)
    - *Postpartum status categories for primary objective:* the following four categories (as agreed with the FDA).
        - ≤ 6 weeks postpartum
        - > 6 weeks and ≤ 14 weeks postpartum

- > 14 weeks and ≤ 52 weeks postpartum
- > 52 weeks postpartum (including women without recorded delivery in the past 52 weeks)

- *Breastfeeding status at the time of IUD insertion:* any evidence of breastfeeding (i.e., any breastfeeding or pumping across a 24-hour period) at the time of IUD insertion was determined based on linked mother/infant records (e.g., well-child visits, infant check-ups, and immunization visits) and clinical notes for the woman and infant. Breastfeeding status was classified as yes (last breastfeeding date within 30 days before IUD insertion or any time after IUD insertion [up to 52 weeks after delivery]), no (last breastfeeding date more than 30 days before IUD insertion or first non-breastfeeding date before IUD insertion), or undetermined. Breastfeeding status was not ascertained for women with no evidence of a live birth in the previous 52 weeks, and these women were not included in analyses related to breastfeeding exposure.
- *IUD type:* three-level categorical variable of inserted IUD type:
  - LNG-IUD: Mirena, Liletta, Skyla, Kyleena
  - Copper IUD: ParaGard, other copper
  - Unknown IUD type
- *Menorrhagia:* diagnosis of menorrhagia was assessed in two variables
  - As an exposure: indicator variable for whether the patient was diagnosed with menorrhagia in the 365 days before the index date (0 = No, 1 = Yes)
  - As a covariate for summary purpose: four-level categorical variable for whether the patient was diagnosed with menorrhagia
    - Diagnosed in the 365 days before the index date, but not diagnosed before that time
    - Not diagnosed in the 365 days before the index date, but was diagnosed before that time
    - Diagnosis recorded both within 365 days before the index date and before that time
    - No diagnosis of menorrhagia within data

9.4.3 Outcome measures

- *Person-time at risk:* calculated from the IUD insertion date until the first occurrence of any of the following: uterine perforation, IUD expulsion, or censoring date.
- *Date uterine perforation confirmed* was the date on which uterine perforation was documented. This may have been complete perforation (with IUD migration into the pelvis or abdominal cavity) or partial perforation (i.e., incomplete, with IUD embedded in the myometrium, visualized as partial perforation on imaging or hysteroscopy, and IUD removed, or partial perforation noted by clinician at time of removal). Cases of both partial and complete perforation were considered under the umbrella term “perforation.” Cases were classified as yes or no.

- *Date IUD expulsion confirmed* was the date on which IUD expulsion was documented. IUD expulsion, which was the unintended, spontaneous expulsion of the IUD, was determined from the EHR, including clinical notes, using algorithms developed during the validation study. Both partial (any portion of IUD in the cervix on imaging or visualized by clinician, or IUD malpositioned on imaging and removed by the clinician) and complete expulsions (IUD located in the vagina, or not present in the uterus or abdomen on imaging, or patient reports IUD fell out) were considered under the umbrella term "expulsion." Cases were classified as yes or no.

If both partial perforation and expulsion (e.g., partial perforation of the *cervix* by the IUD and complete or partial IUD expulsion) occurred and were documented on the same date, then the outcome was classified as both perforation and IUD expulsion, since these outcomes were evaluated separately throughout this study. If both perforation and IUD expulsion occurred for the same IUD insertion but were captured on different dates, then the earlier date constituted a stopping date for assessment of all objectives. No analysis was conducted to assess both perforation and IUD expulsion as a composite outcome or as a subgroup analysis among those with both outcomes.

9.4.4 Additional parameters

Start and stop dates

- *IUD insertion date* was the date on which IUD insertion was documented. This was the starting date (index date) for person-time at risk
- *Beginning date of study period:* the first date EHR data were available from the data source for this study
- *End date of study period:* the last date on which EHR data were available from the data source for this study
- *Date of start of enrollment* (KPNC, KPSC, and KPWA only): the earliest date of enrollment in the health care system for the woman (was used to calculate look-back period)
- *Date of first clinical encounter* (RI only): the earliest in-person visit in the health information exchange data for the woman (was used to calculate look-back period)
- *Date of disenrollment* (KPNC, KPSC, and KPWA only): was the date, after the index date, on which the woman was no longer enrolled in an eligible insurance plan (one gap per year of ≤ 31 days was allowed)
- *Date of last clinical encounter* (RI only): the last date on which a woman had an in-person encounter that was recorded in the health information exchange data
- *Censoring date:* the earliest of the following dates: date of removal of IUD, date of IUD reinsertion, date of start of new pregnancy, hysterectomy date, date of bilateral oophorectomy and other types of sterilization, expiration of IUD (5 years after insertion of Mirena, Kyleena, or unknown IUD, 10 years after insertion for ParaGard and other copper IUDs, 3 years after insertion of Skyla and Liletta), death date, date of disenrollment from the health care system, or date of last clinical encounter in the health care system
    - Expiration of the IUD was operationalized in two ways. The first, used for all analyses, was to add 3 months to the labeled expiration date to allow for the normal variability in clinical visits for removal or replacement of IUDs. The second, used as a sensitivity

analysis for objectives 1 and 2, was to extend the IUD expiration for an additional 2 years based on clinical input that in practice, IUDs are often used for longer than the labeled duration (extended use). The durations for the different brands of IUD are shown in Table 3. For any IUDs where the brand or type was unidentified, the durations assigned were the same as Mirena since it was the most commonly used IUD in the study.

Table 3: Duration of use of IUDs in the study

Approved duration of use by IUD brand during study period	IUD labeled expiration duration	IUD extended use duration
Mirena, 5 years	63 months	87 months
Liletta, 3 or 4 years	51 months	75 months
Skyla, 3 years	39 months	63 months
Kyleena, 5 years	63 months	87 months
Copper IUD, 10 years	123 months	147 months
Unidentified IUD brand (assigned to be same as Mirena)	63 months	87 months

IUD = intrauterine device.

Other parameters

- *Data source:* categorical variable for one of the four data sources included in the study.
- *Continuous enrollment*, in days, that each individual was in the data during the study period was calculated starting on the earliest of date of enrollment (Kaiser Permanente data sources [KPs]) or date of first clinical encounter (RI) and ending on the earliest of date of disenrollment (KPs), date of last clinical encounter (RI), or end date of study period, allowing up to one 31-day gap in enrollment each year to be considered continuously enrolled. The individual's start and end dates in the enrollment files were used for KPNC, KPSC, and KPWA. For RI, the start date was the patient's first clinical encounter within the study period, and the end date was the patient's last observation within the study period. There may be multiple continuous enrollment periods for a woman who moves out of, then back into, the health care plan.
- *Live birth at most recent delivery:* indicator variable for whether the patient had pregnancy ending in live birth within the past 52 weeks (0 = No, 1 = Yes).

9.5 Data sources and measurement

Four data sources with EHRs were used for this study: KPNC, KPSC, KPWA, and RI. Data in different files within each data source were linked by the patient's identification number. Descriptions of the health care system for each source of data follow (Sections 9.5.1 through 9.5.4).

9.5.1 Kaiser Permanente Northern California

The KPNC region in California extends from Santa Rosa and Sacramento in the north, to Modesto in the east, and south to San Jose and Fresno 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 the Medicare patients in the area. The patient population represents the diversity of age, sex, and race/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 datasets—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 datasets via a 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 IUD insertions in this health care system, 67% (more than 100,000) were in women with at least 12 months of continuous enrollment before the date of insertion.

9.5.2 Kaiser Permanente Southern California

KPSC is Kaiser Permanente's largest region, with 4.6 million members who broadly represent the diversity of age, sex, and race/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 datasets 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, as well as member demographics and enrollment information.

Each KPSC member is assigned a unique medical record number upon 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 datasets (both clinical and administrative). The prenatal dataset 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 health care system, 67% (more than 80,000) were in women with at least 12 months of continuous enrollment before the date of insertion.

9.5.3 Kaiser Permanente Washington

Based in Washington state, KPWA (formerly Group Health Cooperative, a nonprofit health system) currently serves approximately 700,000 members and provides primary, specialty, home health, and inpatient skilled nursing care. Members reside in 22 counties in Washington and northern Idaho, and the members in the health care system represent the diversity of age, sex, and race/ethnicity of the geographic region. Approximately 70% of patients receive comprehensive care in KPWA-owned facilities, including 34 primary care medical centers and six specialty medical centers. The remaining 30% receive care from contracted provider networks in geographic areas not served by KPWA medical centers but reimbursed by KPWA.

The EHR system was fully implemented in 2006 and includes datasets on enrollment, encounters, diagnoses, procedures, vital signs, radiology, pathology, laboratory tests, and pharmacy dispensings. Data are linked across all datasets via a unique member identifier. The mother-infant dataset (used to collect breastfeeding data) 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 health care system, 64% (more than 15,000) were in women with at least 12 months of continuous enrollment before the date of insertion.

9.5.4 Regenstrief Institute

RI has research access to the Indiana Health Information Exchange, which has served over 17 million patients and includes clinical data from 103 Indiana hospitals, 41 core hospital systems, 60 community clinics, and the state and local public health departments of Indiana, representative of the demography of Indiana, particularly the urban areas. Data from health care encounters are available for this study since 2001 and are captured in a standardized fashion for inpatient admission/discharge information; outpatient visit information; laboratory values; microbiology, pathology, radiology, and cardiology reports; and clinical notes. Data from the datasets are linked via a unique identifier across institutions.

In the validation study, continuous enrollment was measured via health care encounters. Of all IUD insertions in this health care system, 74% (~5,700) were in women with at least one clinical encounter 12 months or more before the date of insertion.

9.6 Bias

Sensitivity analyses and other design elements were evaluated to assess whether the following decisions regarding specific design elements could have introduced bias:

- Extending the IUD expiration date (IUD extended use) was used in censoring to ensure that outcomes were not excluded differentially in the assessment of uterine perforation in association with breastfeeding at IUD insertion and postpartum timing of IUD insertions. Even though it seemed unlikely that uterine perforations would occur later in one group versus another, we thought it prudent to do this analysis.
- Analyzing only first recorded IUD insertions in the primary analyses to ensure independence of observations.
- Analyzing subsequent insertions to determine whether associations between exposures and outcomes were similar or different.
- Conducting data extraction and analyses by different parties. Exposures, outcomes, and covariate variables were extracted by research partners, while analyses were conducted by RTI-HS after data extraction was completed.
- Conducting research site-specific analyses to examine the patterns of exposure-outcome associations to ensure that one of the sites did not have undue influence. Also, an analysis was done where a research site x exposure interaction term was included in the models to ascertain whether there were statistically significant differences among the research sites in the association between each outcome and exposure.

9.7 Study size

The sample size/power calculations for this study used data on the incidence of outcomes and frequency of exposures from sources described below. Uterine perforation is an uncommon event, with 81 uterine perforations reported among 61,448 women over 12 months after insertion of either an LNG-releasing or copper IUD (1.3 cases per 1,000 IUD insertions) in EURAS-IUD [2]. EURAS-

IUD found that the risk was higher in breastfeeding women (5.3 per 1,000 insertions) than in those not breastfeeding (0.9 per 1,000 insertions) and in women with early (≤ 36 weeks) postpartum insertion (5.6 per 1,000 insertions) than later (> 36 weeks) postpartum insertion (1.6 per 1,000 insertions) [12]. About 11% of the women in EURAS-IUD were breastfeeding, and approximately 20% had an IUD insertion at ≤ 36 weeks postpartum [12].

Approximately 325,000 IUD insertions were identified during the time frame of the APEX IUD validation/feasibility study (end date, 30 September 2015), and approximately 65% of those occurred after at least 12 months within the data source. In approximately 90% of IUD insertions, this was the first observed insertion for each woman. Approximately 30% of women were identified as having an IUD inserted within the first 52 weeks postpartum. Based on these results and some assumptions—approximately 3 years of data in addition to the data used in the validation study and allowing for a loss of approximately 15% of the insertions due to missing data and the propensity score trimming process (Section 9.9.2.4.2)—the number of first insertions of an IUD available through June 2018 from the four health care systems was anticipated to be approximately 225,000, with breastfeeding status available for approximately 60,000. For the two primary objectives related to the risk of uterine perforation, the power of the study was calculated for differences in the estimated risk of uterine perforation with respect to (1) breastfeeding status at the time of IUD insertion and (2) time interval of the IUD insertion following delivery.

The null hypothesis to be tested for primary objective 1 was that the natural logarithm of the adjusted summary perforation HR for breastfeeding versus not breastfeeding at the time of IUD insertion was equal to 0. Using information from the validation study, the expected allocation ratio of breastfeeding versus not breastfeeding was 60:40 for this objective. Three null hypotheses to be tested for primary objective 2 were that the natural logarithm of the adjusted summary perforation HRs for early (i.e., ≤ 6 weeks postpartum, > 6 and ≤ 14 weeks, > 14 and < 52 weeks) versus later (i.e., > 52 weeks) postpartum IUD insertion were equal to 0. Based on information from the validation study, the expected allocation ratio of the corresponding postpartum period categories was 5:20:5:70 for this objective.

Power calculations for the expected number of IUD insertions were performed using PASS 14 software (NCSS, LLC, Kaysville, Utah) for a two-sided test of the HR [13]. Table 4 indicates the power to detect various HRs at the two-sided $\alpha = 0.05$ significance level based on a perforation risk of 1.3 per 1,000 insertions and the percentage of insertions expected for the exposure groups of interest, i.e., breastfeeding versus not breastfeeding and early versus late postpartum insertion for the two cutpoints of interest.

Table 4: Power to detect hazard ratio for uterine perforation based on anticipated number of IUD insertions and exposure group allocation

Exposure group	Number of insertions expected	Allocation % (exposed: unexposed)	Hazard ratio that can be detected (% power)				
			1.5	1.75	2.0	2.25	2.5
Primary objective, 1: Breastfeeding vs. not breastfeeding	60,000	60:40	42	68	85	94	98
Primary objective, 2: Categories of postpartum insertion timing: ≤ 6 weeks vs. > 52 weeks, including women without a recorded delivery within the past 52 weeks	168,750	5:70	32	54	73	85	92
Primary objective, 2: Categories of postpartum insertion timing: > 6 and ≤ 14 weeks vs. > 52 weeks, including women without a recorded delivery within the past 52 weeks	202,500	20:70	78	97	> 99	> 99	> 99
Primary objective, 2: Categories of postpartum insertion timing: > 14 weeks and ≤ 52 weeks vs. > 52 weeks, including women without a recorded delivery within the past 52 weeks	168,750	5:70	32	54	73	85	92

IUD = intrauterine device.

Table 5 displays the power to detect various HRs at the two-sided $\alpha = 0.05$ significance level for the risk of perforation among LNG-releasing versus copper IUDs based on a perforation risk of 1.3 per 1,000 insertions and the percentage of insertions expected for the exposure groups of interest, i.e., timing of postpartum insertion and breastfeeding versus not breastfeeding.

Table 5: Power to detect hazard ratio for uterine perforation for LNG versus copper IUDs based on anticipated number of IUD insertions and an 80% (LNG) versus 20% (copper) exposure group allocation

Exposure group	Number of insertions expected	Hazard ratio that can be detected (% power)				
		1.5	2.0	3.0	4.0	5.0
LNG-IUD vs. copper IUD	225,000	79	> 99	> 99	> 99	> 99
LNG-IUD vs. copper IUD for postpartum insertion ≤ 6 weeks	11,250	9	18	39	56	69
LNG-IUD vs. copper IUD for postpartum insertion > 6 weeks and ≤ 14 weeks	45,000	24	56	92	99	> 99
LNG-IUD vs. copper IUD for postpartum insertion > 14 weeks and ≤ 52 weeks	11,250	9	18	39	56	69
LNG-IUD vs. copper IUD for postpartum insertion > 52 weeks	157,500	64	98	> 99	> 99	> 99
LNG-IUD vs. copper IUD for breastfeeding at the time of insertion	36,000	20	47	85	97	> 99
LNG-IUD vs. copper IUD for not breastfeeding at the time of insertion	24,000	15	34	69	87	95

IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.

9.8 Data transformation

This study used data previously collected in EHRs and other electronic administrative and clinical data sources at the four research sites. Personal identifiers were removed at the sites, and the data from each site were sent to RTI-HS for analysis.

Data management was conducted in accordance with standard operating procedures developed for the study and used across all sites. Routine procedures included checking electronic files, maintaining security and data confidentiality, following the statistical analysis plan, and performing quality-control checks of all programs. All analyses, including conversion of the original data to analysis variables at each site, were performed using SAS software, version 9.3 or higher (SAS Institute, Inc., Cary, North Carolina).

Specifics from each data source are described in Sections 9.8.1 through 9.8.4.

9.8.1 Kaiser Permanente Northern California

The Kaiser Permanente health plan maintains comprehensive electronic administrative and clinical databases that are linked to the individual member through a unique medical record number assigned at enrollment. Medical record numbers are not re-issued after a member leaves the health plan; therefore, linkage is assumed to be 100%.

At KPNC, deployment of the EHR system (called HealthConnect from Epic) began in 2005, with complete deployment across all sites by 2009 (2008 for outpatient and 2009 for inpatient). Data were housed in a Clarity database, which is a relational database residing on a Teradata/Exadata) platform and consisting of thousands of tables that can be linked by various primary keys, such as medical record number, patient identification (ID), encounter ID, medication ID, diagnosis ID, procedure ID. Teradata/Exadata SQL/MR was used to extract data from these various tables; further

data manipulation was done either in SQL (structured query language) or in SAS version 9.3 or higher.

In addition, data were also managed within the Division of Research (DOR) Virtual Data Warehouse (VDW). The VDW resides on an Oracle platform and was also available as SAS datasets on a secure UNIX server. The VDW pools together data from various sources to bring together both Epic and pre-Epic data and includes clinical, demographic, enrollment, census, and mortality information.

Data were extracted from Clarity-based tables, as well as the in-house DOR VDW and archived databases. As inclusion and exclusion criteria were applied to build the cohort, all relevant cohort-defining datasets were saved on the secure DOR servers that were backed up every day by the DOR information technology (IT) department. Every analyst in DOR was assigned a secure space by DOR IT security on several servers that could be accessed only by that analyst. In addition, analysts had shared space on these secure servers that could be accessed only by relevant project members. DOR IT security was responsible for providing the governance, guidance, and tools to protect confidential and nonpublic Kaiser Permanente information. DOR IT partnered with the National Compliance Organization, Technology Risk Organization, and The Permanente Medical Group to lay the foundation for operational strategies and programs that met Kaiser Permanente's security obligations and positioned DOR to become an industry leader in research information security.

Access to the EHR required authorization from KPNC IT to conduct medical record review validation of electronically extracted data. Each clinician, DOR programmer analyst, and medical record analyst was required to enter a unique password assigned to them to access the EHR. Access to EHR records expired in 90 days if unused. Reapplication to DOR IT or KPNC IT was required to regain EHR access.

9.8.2 Kaiser Permanente Southern California

The KPSC EHR system (HealthConnect) was fully implemented in 2008. The database systems at KPSC consist of the Oracle and Teradata platforms. As of January 2018, the majority of the data marts reside in the Oracle database system. The Teradata system is being used for data marts that require faster data retrieval capabilities (millions of records in seconds). The Teradata system is a Massively Parallel Processing system in which partitioned data in each Access Module Processor (AMP) can be processed independently. The Teradata system is hosted by Kaiser Permanente Information Technology and has a total of 1,320 AMPs.

The back-end database, Clarity, is the primary source of patient encounter data beginning in 2005. The research team at KPSC extracted Clarity, legacy, and claims data and integrated them with historical data before HealthConnect into a comprehensive Research Data Warehouse (RDW) that is saved in Oracle. The RDW contains information on all utilizations within the KPSC system, including date and site of care, diagnosis codes, procedure codes, vaccinations, vital signs, prescription medications, radiology reports, clinical reports, laboratory results, as well as member demographics and enrollment information. The RDW is updated weekly.

KPSC also built and maintains a VDW based on the RDW to support collaborative studies across various research networks. The RDW and VDW are stored on a secure UNIX server. This server is kept in a secure facility with multiple power sources and backup power provision. All data stored on this server are backed up nightly. Access to the RDW and VDW is limited to authorized programmers and statisticians within the Department of Research and Evaluation.

Natural language processing, a field of computer-science methods aimed at standardizing and analyzing free text, was also used to convert information residing in natural language into a more structured format. NLP was performed through Python programming language (V 3.6 with standard packages) on a high-performance dedicated NLP Linux server. Custom Python programs were written to optimize the search and analysis of unstructured clinical notes in the identification of variables of interest for this study.

The research team at KPSC managed the study data and provided the support needed to meet study objectives. The analyst/programmer performed routine range and consistency checks.

This study used administrative data and electronic medical records. Procedures mandated by the institutional review board (IRB) and the Health Insurance Portability and Accountability Act (HIPAA) for the protection of confidentiality for patient data were carefully followed. The analysis datasets created by the KPSC study team were stored and archived at KPSC as per the applicable requirements and retention policies. Computer files associated with this project were kept in a password-protected environment. If hard copies of the data were generated for the study, they were stored in locked file cabinets accessible only to the investigators and KPSC study staff. All reports and published results from this study were limited to statistical compilations of the data that did not identify individual patients. Only aggregate data and summary tables, which did not contain patient-level information, were reported and shared with the sponsor. The KPSC principal investigator was responsible for ensuring that KPSC policies and procedures for confidentiality and security were followed for this project.

9.8.3 Kaiser Permanente Washington

In collaboration with RTI-HS, Bayer, and the other participating research sites, the KPWA study team identified the study variables of interest (exposure, outcomes, additional covariates) to accomplish the study aims and perform requisite analyses. The project team, led by the analyst and programmer, developed the programming specifications. To create the study dataset, the programmer developed the code to extract data from the existing health plan administrative data, which accessed the health plan's EHR Clarity database and the KPWA VDW. No direct contact with health plan members occurred. The programming and creation of raw and analytic data files was done in SAS version 9.4. Custom NLP programs were written in Python to supplement the structured data with information from clinical text. A data collection form for review/validation of outcomes, breastfeeding status, and IUD removal from the EHR was developed using standard software and helped inform NLP. All perforations identified through EHR were validated with chart abstraction. All study data were stored in secure computing locations within KPWA Health Research Institute that were backed up nightly. Prior to any data collection, all study protocols were submitted for review and received approval from the KPWA IRB. Once the project datasets were created, the analytic files were deidentified at the individual level, and each woman was identified only by a study ID.

The quality of KPWA data was assessed and improved through two mechanisms: dedicated quality-assurance programming and crowdsourcing via the VDW user base. Workgroups were responsible for authoring quality-assurance programs that assessed adherence to the VDW data model and identified anomalies in the data. These quality checks ranged from verifying the existence of variables and assuring that they contained permissible values to more sophisticated analyses requiring clinical or scientific knowledge that compared rates and trends of events across institutions. Due to the long-term use of the VDW, this crowdsourced quality-assurance approach

effectively identified data anomalies. Site data managers investigated these anomalies and reported resolutions in the issue tracker.

The programs that selected the study data from the health plan data sources were reviewed by the analyst and study team once the programs had been created and again as data became available. As they were created, the datasets were checked by the programmer for range values, consistency, and completeness. The Python code used for NLP was reviewed and tested by the programmer and study team, and the extracted data were verified through manual review.

9.8.4 Regenstrief Institute

Data for this study came from both structured data (ICD-9,† ICD-10,‡ Current Procedural Terminology, and Healthcare Common Procedure Coding System codes and National Drug Codes) and unstructured data from clinical notes. The NLP pipeline developed by RI to analyze unstructured data had tools to pull relevant notes for specified cohorts, techniques to find all related terms/synonyms, an approach to reducing "false-positive" hits through exclusion of negation (e.g., not uterine perforation) and family history, and a validation tool built in to add structured data back to the dataset. Data from the various institutions that contributed to the health information exchange are stored separately, but patient records are linkable across all sources via a global medical record number. The data are updated nightly. The data manager had access to the source data once IRB approval was granted. Chart reviewers could see identified data, if necessary.

RI's personnel have been trained in methods to protect patient confidentiality, and efforts were made to minimize the risk to patients as data were extracted and analyzed. RI's secure servers were protected by a firewall, and only deidentified data were shared by the data analyst with the study team.

9.9 Statistical methods

An overview of the data analysis can be found below. General statistical analyses and methodology for this study are presented first, followed by specific data analyses related to each objective. A detailed description of variable definitions, planned analyses, and display specifications were included within the statistical analysis plan. Statistical tests were conducted on the assumption that residual confounding could be neglected. However, the validity of this assumption could not be assessed within the framework of this study.

Research partners at each site created a deidentified analytic dataset that was shared with RTI-HS. Analyses related to primary and secondary objectives were performed at the coordinating center (RTI-HS) on the deidentified patient-level data from all four health care systems. In addition to the pooled results, the results for each objective were presented separately for each site, with one exception (for IUD type) described in the following sections.

9.9.1 Main summary measures

The descriptive analyses for all variable were done as described below.

Crude incidence rates and cumulative incidence using person-time as the denominator were calculated for all study cohorts and within levels of exposure variables for both outcomes.

† ICD-9 = *International Classification of Diseases, 9th Revision.*
‡ ICD-10 = *International Classification of Diseases, 10th Revision.*

Crude and adjusted IRRs and IRDs were calculated for uterine perforation and IUD expulsion by postpartum timing of IUD insertion (≤ 36 weeks vs. > 36 weeks). Crude and adjusted HRs (HRs) were calculated for all exposure/outcome combinations and the specified interactions in objectives 28 through 32.

9.9.2 Main statistical methods

9.9.2.1 Study cohorts of interest

The complete study population was defined by the study inclusion and exclusion criteria. However, subgroups of the complete study cohort were used to address certain study objectives. The study cohorts of interest are outlined in Section 9.9.2.1.1.

9.9.2.1.1 Study cohorts defined by exposure variables

Only women with eligible IUD insertions and nonmissing exposures were included in analyses reliant on exposure status. Three cohorts of interest were defined based on need for nonmissing data:

- *Complete study population:* all first IUD insertions included in the data[§] based on study inclusion and exclusion criteria outlined in Section 9.2.2. This study cohort included women with missing data for breastfeeding status or IUD type or both.[**]
- *Breastfeeding:* all IUD insertions among women who were no more than 52 weeks postpartum at the time of IUD insertion and had either "yes" or "no" breastfeeding status at the time of IUD insertion were included in this cohort. IUD insertions among women with undetermined breastfeeding status were not included.
- *IUD type:* all IUD insertions with a known type of IUD (either LNG-IUD or copper IUD) were included in this cohort. IUD insertions among women with an undetermined IUD type were not included.

[§] Objectives 18 and 26 were the only objectives that assessed subsequent IUD insertions. Analyses for all other objectives assessed only the first IUD insertion in the data for each woman.

[**] No missing data were anticipated for postpartum/no delivery status or menorrhagia. For both of these variables, lack of documentation associated with the variable would default the status for that IUD insertion to the unexposed or referent category of the variable.

9.9.2.2 Descriptive analyses

Descriptive analyses of each variable were conducted before other analyses.

Descriptive analyses for all variables of interest defined in Section 9.4, are presented overall and within each data source for the study cohort.[††] For categorical variables, frequencies and percentages are presented for each level. Continuous variables are summarized by the mean, standard deviation, minimum, maximum, median, and quartiles. The proportion of missing data is captured for each variable.

Study cohort at baseline

Descriptive statistics were obtained for study cohorts at baseline, including overall and within each of the following exposure groups:

- Breastfeeding status (yes, no, undetermined)
- Postpartum period (using the four postpartum status variables defined in Section 9.4.2)
- IUD type (i.e., LNG or copper)

Outcomes

Characteristics of patients experiencing outcomes were presented for each study outcome. Characteristics included frequencies and percentages for each level of each outcome (including not experiencing the outcome) and by demographics and clinical characteristics of patients at the time of IUD insertion.

9.9.2.3 Crude incidence rates and crude cumulative incidence

9.9.2.3.1 Crude incidence rates

While the main study analyses accounted for the anticipated underlying change in risk of outcomes across the time women were exposed to inserted IUDs, constant incidence rates were also calculated across the person-time women contributed to the study. Following characterization of variables, person-time at risk and crude incidence rates of outcomes were calculated. Crude incidence rates were assessed rather than incidence proportions, since patients contributed variable time at risk to the study. Crude incidence rates were calculated for all study cohorts and within levels of exposure variables.

Crude incidence rates were calculated as the number of outcomes occurring during the person-time at risk divided by the total person-time at risk (in person-years). Crude incidence rates were reported as point estimates (number of cases per 1,000 person-years) and 95% CIs.

[††] Descriptive and comparative analyses for all variables of interest are presented overall and stratified by data source, with the exception of IUD type. The variable IUD type was analyzed by data source, but only the data source and RTI-HS had access to the data source specific information. Data included in this report present IUD type aggregated over all data sources. Additionally, analyses for objectives 18 and 26 are presented by data source only if there are more than 20,000 subsequent IUD insertions for that research site; however, all subsequent insertions were included in the pooled analysis.

9.9.2.3.2 Crude cumulative incidence

Crude estimates of the cumulative incidence, defined as number of outcomes occurring up to a time point out of the number of IUD insertions, were estimated using the Kaplan-Meier method. The corresponding curve over time, also known as the failure function (i.e., 1-survival function), was plotted. Crude cumulative incidence was estimated and plotted for all study cohorts and within levels of exposure variables.

9.9.2.4 Crude and adjusted hazard ratios

9.9.2.4.1 Crude hazard ratios

In binary comparisons, Cox regression models were used to estimate crude HRs for the exposed group (e.g., breastfeeding at the time of IUD insertion) relative to the referent group (e.g., not breastfeeding at the time of IUD insertion). In categorical comparisons, Cox regression models were used to estimate crude HRs for each exposure group (e.g., IUD insertion ≤ 6 weeks postpartum) relative to the referent group (IUD insertion > 52 weeks postpartum). These crude HRs were calculated for each outcome without adjustment for covariates. All crude HRs were reported as point estimates with 95% CIs.

The proportional hazards assumption between each exposure and outcome pairing was assessed using visual examination of hazard functions, log-log survival curves, and goodness-of-fit testing using Schoenfeld residuals [14]. For violations of the proportional hazards assumption, time-dependent exposure covariates were included in crude and adjusted HR models by fitting interaction terms with continuous or categorical time. Additional details are included in the statistical analysis plan.

9.9.2.4.2 Control for confounding effects

Confounding was controlled through the use of propensity scores, based on the values of covariates at the time of IUD insertion. Propensity scores estimate the probability that a given patient was exposed conditional on measured covariates and can serve as a summary confounder variable. Propensity scores can perform better than conventional regression methods when the number of events relative to the number of potential confounders is small, because rather than having to model the outcome events with a model that includes many predictor variables, which may lead to overfitting of the outcome model, one can instead model the exposure, for which the larger number of exposed people provides sufficient data to accommodate a model with a large number of confounders [15]. This advantage was important in this study, given the low number of expected events, particularly for uterine perforation.

Separate propensity score models were developed for exposure-outcome pairings related to the primary objectives, IUD type, and menorrhagia. Additionally, separate propensity score models were developed for assessment of first observed IUD insertions and for assessment of subsequent IUD insertions. Thus, 16 propensity score models were developed to assess exposures: 8 for models including first observed IUD insertions and 8 for models including subsequent IUD insertions (Table 6). One propensity score model was also developed to assess the interaction between breastfeeding and early versus late postpartum IUD insertion. This yielded a total of 17 propensity score models for this study.

Table 6. Propensity score models for postmarketing requirement study defined by exposure and outcomes of interest

Model number	Exposure (dependent variable of propensity score model)	Outcome (not included in propensity score model)
1 (primary objective)	Breastfeeding status (yes vs. no)	Uterine perforation
2 (primary objective)	Postpartum insertion (4 categories)[a]	Uterine perforation
3	IUD type (LNG-releasing vs. copper)	Uterine perforation
4	Menorrhagia (yes vs. no)	Uterine perforation
5	Breastfeeding status	IUD expulsion
6	Postpartum insertion (4 categories)[a]	IUD expulsion
7	IUD type (LNG-releasing vs. copper)	IUD expulsion
8	Menorrhagia (yes vs. no)	IUD expulsion
9	Interaction of breastfeeding and early vs. late postpartum timing of IUD insertion (breastfeeding/≤ 14 weeks; breastfeeding/> 14 weeks; no breastfeeding/≤ 14 weeks; no breastfeeding/> 14 weeks [referent])	Uterine perforation

IUD = intrauterine device; LNG = levonorgestrel.

Note: Models 1-8 were run in the dataset containing first observed IUD insertions and separately in a dataset containing subsequent IUD insertions.

[a] Secondary objectives included dichotomization of “early” and “late” postpartum categories. Separate propensity score models were not *developed* for these objectives. Rather, the propensity scores calculated with the four-category variable were used, and the distribution of scores were collapsed into the categories for each secondary objective. Assessment of distributions of propensity scores was performed within these collapsed categories.

Propensity scores for dichotomous exposure variables were estimated by fitting a logistic regression model that incorporated data source (KPNC, KPSC, KPWA, or RI) and measured potential predictors of exposure as independent variables (all baseline variables in Section 9.4.1 were considered). The dependent variable in the propensity score model was exposure status (e.g., women breastfeeding at the time of IUD insertion vs. not breastfeeding at the time of IUD insertion).

Propensity scores for the categorical variable timing of postpartum insertion were estimated by fitting a multinomial logistic regression model that incorporated data source (KPNC, KPSC, KPWA, or RI) and measured potential predictors of exposure as independent variables (all baseline variables in Section 9.4.1 were considered). The dependent variable in the propensity score model was exposure category (i.e., ≤ 6 weeks postpartum, > 6 and ≤ 14 weeks postpartum, > 14 and ≤ 52 weeks postpartum, > 52 weeks postpartum [referent]).

Covariates were assessed for inclusion in propensity score models based on association with the study outcome [16] and thus were not outcome-blinded. Categorical variables were assessed for inclusion based on indicator coding of the categories. Continuous variables (including integer count variables) were assessed for inclusion as continuous, dichotomous, and categorical variables, as appropriate. Covariates were included in the propensity score model if the crude HR was greater than 1.11 or less than 0.90. Additional confounders were selected for inclusion within propensity score models if at least a 10% change in the HR of the exposure-outcome relationship occurred when adjusting for that variable, including at least a 10% change in any level of a categorical exposure variable relative to the referent group.

From the fitted logistic regression models, propensity scores were estimated for each IUD insertion. The distribution of propensity scores among categories (e.g., breastfeeding at the time of IUD insertion versus not breastfeeding at the time of IUD insertion) were examined.

The propensity scores were used to calculate weights for each IUD insertion within each exposure group. The weights were “overlap weights” [17]. This method has an advantage of not requiring trimming of observations, rather observations where there is significant overlap between groups are up-weighted and observations where there is very little overlap are down-weighted To assess whether covariates were balanced across exposure groups after weighting, the distribution of each variable was compared between categories of the exposure variable, and balance parameters (i.e., standardized differences) [18] were calculated. Pairwise balance parameters (i.e., pairwise standardized differences) were used for the categorical exposure variable (postpartum timing) in which each category was compared to the referent group. The balance between exposure groups was assessed overall and within each data source. If the groups were unbalanced on key covariates after application of overlap weighting, then the logistic regression model was revised by including interaction terms (e.g., with data source), higher order terms, or transformation of variables, as needed, and the covariate balance between the groups overall and within each data source was re-evaluated based on the revised model [19,20]. When satisfactory balance between the exposed and unexposed groups was achieved (in general, absolute standardized difference < 0.2), the weighting was incorporated in modeling for confounder-adjusted outcome assessments (Section 9.9.2.4.3).

9.9.2.4.3 Estimation of confounder-adjusted effect measures

The adjusted HRs and 95% CIs for outcomes between exposure groups were estimated using weighted Cox regression models with effects for exposure status and interaction with site (as appropriate). Time-dependent exposure covariates were included if violation of the proportional hazards assumption was identified in the unweighted Cox model (described in Section 9.9.2.4.1). Hazard ratios were adjusted for possible confounding effects using overlap weighting (Section 9.9.2.4.2). If breastfeeding status, postpartum timing, or IUD type were not included within a propensity score (as independent variables when not the dependent variable), then a separate Cox model also including these variables as covariates were developed. Adjusted HRs were reported as point estimates with 95% CIs. For any models including time-dependent exposure covariates, separate adjusted HRs were reported for the estimates of the effect of the exposure over time.

9.9.2.5 Crude and adjusted IRR and IRD

9.9.2.5.1 Crude IRR

Crude IRRs were estimated for the exposed group(s) (e.g., breastfeeding at the time of IUD insertion) relative to the referent group (e.g., not breastfeeding at the time of IUD insertion) from measures obtained in Section 9.9.2.3.1. Crude IRRs were calculated as the crude incidence rate in the exposed divided by the crude incidence rate in the unexposed. These crude IRRs were calculated for each outcome without adjustment for covariates. All crude IRRs were reported as point estimates with 95% CIs.

9.9.2.5.2 Crude IRD

Crude IRD was estimated for the exposed group(s) (e.g., breastfeeding at the time of IUD insertion) relative to the referent group (e.g., not breastfeeding at the time of IUD insertion) from measures obtained in Section 9.9.2.3.1. Crude IRD was calculated as the crude incidence rate in the exposed minus the crude incidence rate in the unexposed. These crude IRDs were calculated for each

outcome without adjustment for covariates. All crude IRDs were reported as point estimates with 95% CIs.

9.9.2.5.3 Adjusted IRR

The IRR, was adjusted for possible confounding effects via weighted estimation of the rates using overlap weights (Section 9.9.2.4.2) derived from the same propensity score models as those developed for adjustment of the HRs. Adjusted IRR was calculated as the weighted incidence rate in the exposed divided by the weighted incidence rate in the unexposed referent. If breastfeeding status, postpartum timing, or IUD type were not included within a propensity score model (as independent variables when not the dependent variable), then the adjusted IRR, included adjustment for these variables as strata and was calculated using the Mantel-Haenszel approach outlined in Rothman et al. [21]. Adjusted IRR was reported as point estimates with 95% CIs.

9.9.2.5.4 Adjusted IRD

The IRD was adjusted for possible confounding effects via weighted estimation of the rates using overlap weights (Section 9.9.2.4.2) derived from the same propensity score models as those developed for adjustment of the HRs. The adjusted IRD was calculated as the weighted incidence rate in the exposed minus the weighted incidence rate in the unexposed referent. If breastfeeding status, postpartum timing, or IUD type were not included within a propensity score model (as independent variables when not the dependent variable), then the adjusted IRD included adjustment for these variables as strata and was calculated using the Mantel-Haenszel approach outlined in Rothman et al. [21]. Adjusted IRDs were reported as point estimates with 95% CIs.

9.9.3 Missing values

Missing data were treated as missing, and no imputations were performed. Where appropriate, variables included a “missing” category for analyses. Consequently, data analyses were conducted using all women and all insertions to the extent possible with respect to their observed available data (i.e., the IUD insertion was not included in an analysis if data were missing for any variable in that analysis, except where “missing” was a separate category for the variable); the percentage of women or insertions with missing data was provided for key variables of interest.

Counts of missingness were reported in descriptive analyses of categorical variables, and percentages for the nonmissing categories were based on the number of nonmissing values. For continuous variables, the number of nonmissing values was reported, and descriptive summaries were based on the number of nonmissing values.

9.9.4 Study objective–specific data analysis

9.9.4.1 Analyses of primary objectives

To address the primary objectives 1 and 2 in Section 7.1, the primary endpoints in the study were the adjusted HRs for uterine perforation among the following groups of women (Table 7):

1. Women who were ≤ 52 weeks postpartum with breast feeding status who were breastfeeding at the time of the first observed IUD insertion versus those who were not breastfeeding at the time of the first observed IUD insertion.
2. Women who had a first observed IUD insertion in different time periods postpartum (i.e., ≤ 6 weeks, > 6 weeks and ≤ 14 weeks, > 14 weeks and ≤ 52 weeks) versus those who had a first observed IUD insertion late in the postpartum period (more than

52 weeks postpartum, including those without recorded delivery in the previous 52 weeks).

Table 7. Relevant primary objectives, by study cohort

Objective number	Brief description	Complete study population	Within 52 weeks of delivery and breastfeeding status available	IUD type available
1	By breastfeeding status		X	
2	By postpartum category	X		

IUD = intrauterine device.

Adjusted HRs were developed for each group of women as described in Section 9.9.2.4.3. Additionally, the statistical interaction effect between the data source and the exposure was assessed after confounding adjustment. The statistical interaction was assessed by including terms for exposure, data source, and the statistical interaction between data source and exposure in the weighted Cox models. A type 3 group test for the statistical interaction terms was conducted. If the test was statistically significant ($P < 0.05$), then the interaction terms were retained in the final model, and the adjusted HRs were reported for each data source. If the interaction terms were not deemed significant, then the interaction terms were removed, and the overall adjusted HRs (the main effect) were reported as the results of the primary analyses. For interpretation purposes, the overall adjusted HRs were reported even though the statistical interaction was significant.

Two-sided 95% CIs of the adjusted HRs for uterine perforation are presented, and a two-sided overall test of the null hypothesis that the natural logarithm of the adjusted HR equaled 0 was performed for each of the primary objectives.

The null hypothesis tested for primary objective 1 was that the natural logarithm of the adjusted HR for uterine perforation in breastfeeding women versus women who were not breastfeeding at the time of first observed IUD insertion was equal to 0 (i.e., HR was equal to 1). A P value ≤ 0.05 for this test would reject the null hypothesis of no difference in the adjusted HR among breastfeeding women versus women who were not breastfeeding at the time of first observed IUD insertion, indicating there was a difference in the risk of uterine perforation among breastfeeding women versus women who were not breastfeeding at the time of first observed IUD insertion; a P value > 0.05 indicated insufficient evidence of a difference in the risk of uterine perforation among breastfeeding women versus women who were not breastfeeding at the time of first observed IUD insertion.

The null hypothesis tested for primary objective 2 was that the natural logarithm of the adjusted HR for uterine perforation in women with IUD insertion within different time periods postpartum (i.e., ≤ 6 weeks, > 6 weeks and ≤ 14 weeks, > 14 weeks and ≤ 52 weeks) versus late postpartum IUD insertion (i.e., > 52 weeks postpartum or no recorded delivery within the past 52 weeks) was equal to 0 (i.e., HRs were equal to 1). A P value ≤ 0.05 for these tests would reject the null hypothesis of no difference in the adjusted summary HRs for an early category versus later postpartum IUD insertion, indicating a difference in the risk of uterine perforation for the early category versus later postpartum IUD insertion; a P value > 0.05 indicates insufficient evidence of a difference in the risk of uterine perforation for the early category versus later postpartum IUD insertion. There was no adjustment for multiplicity.

As a sensitivity analysis, confounding effects were accounted for by including selected key covariates in the unweighted Cox models. Due to the sparse outcomes, limited covariates were selected for inclusion based on their association with the study outcome.

In addition, crude HRs (Section 9.9.2.4.1) were reported overall and by data source (with the exception of the HR for IUD type, which was reported only overall).

9.9.4.2 Analyses of secondary objectives for incidence rates and cumulative incidence

Estimation of crude incidence rates and crude cumulative incidence was conducted for secondary objectives 3 to 12 in Section 7.2.

First, crude incidence rates and crude cumulative incidence were calculated as described in Section 9.9.2.3. These measures were assessed within relevant cohorts of interest as indicated by "X" in Table 8. The crude cumulative incidence was plotted overall for each outcome (objectives 3 through 12).

Table 8. Study cohorts relevant to objectives for incidence rates and cumulative incidence

Objective number	Brief description	Complete study population	Within 52 weeks postpartum and breastfeeding status available	IUD type available
3	Overall	X	X	
4	By postpartum category	X		
5	By breastfeeding status		X	
6	By IUD type			X
7	By menorrhagia	X		
8	Overall	X	X	X
9	By postpartum category	X		
10	By breastfeeding status		X	
11	By IUD type			X
12	By menorrhagia	X		

IUD = intrauterine device.

9.9.4.3 Analyses of difficult insertion

The prevalence of indicators of a difficult insertion (objective 13) is presented via contingency tables (Difficulty = yes, no) including frequencies and percentages of each level of each exposure and outcome variable.

9.9.4.4 Analyses of comparative secondary objectives

9.9.4.4.1 Comparing adjusted hazard ratios for uterine perforation and IUD expulsion among first observed IUD insertions

Estimation of adjusted HRs associated with the first observed IUD insertions was conducted for secondary objectives 14 to 16, 19 to 24, and 27 in Section 7.2 using the same analysis approach as that used for primary objectives.

Crude HRs (Section 9.9.2.4.1) were also estimated. These measures were assessed within relevant cohorts of interest as indicated by "X" in Table 9.

Table 9. Study cohorts relevant to comparative objectives

Objective number	Brief description	Complete study population	Within 52 weeks postpartum and breastfeeding status available	IUD type available
Adjusted hazard ratio for uterine perforation				
14	By early (< 14 weeks) vs. late (≥ 14 weeks) postpartum	X		
15	By ≤ or > 36 weeks postpartum	X		
16	By IUD type			X
19	By menorrhagia	X		
Adjusted hazard ratio for IUD expulsion				
20	By breastfeeding status		X	
21	By early (≤ 14 weeks) vs. late (> 14 weeks) postpartum	X		
22	By ≤ or > 36 weeks postpartum	X		
23	By postpartum category	X		
24	By IUD type			X
27	By menorrhagia	X		

IUD = intrauterine device.

9.9.4.4.2 Comparing adjusted IRR and adjusted IRD for uterine perforation and IUD expulsion among first observed IUD insertions

Estimation of adjusted IRR, and IRD associated with the first observed IUD insertions within the data was conducted for secondary objectives 17 and 25 in Section 7.2 to assess the change in rate of uterine perforation and IUD expulsion associated with early versus late postpartum IUD insertion (with a cut point at 36 weeks). For these analyses, follow-up data were truncated at 1 and 5 years to provide an analytic approach similar to that seen in EURAS-IUD.

Crude IRR, and IRD were generated from the crude incidence rates obtained for objectives 4 and 9 and were developed as described in Sections 9.9.2.5.1 and 9.9.2.5.2. After adjustment via weighting, adjusted IRR, and IRD with associated 95% CIs were calculated for each outcome as described in Sections 9.9.2.5.3 and 9.9.2.5.4. These measures were assessed within relevant cohorts of interest as indicated by “X” in Table 10.

Table 10. Study cohorts relevant to IRR, and IRD in comparative objectives

Objective number	Brief description	Complete study population	Within 52 weeks postpartum and breastfeeding status available	IUD type available
Adjusted hazard ratio for uterine perforation				
17	By ≤ or > 36 weeks postpartum	X		
Adjusted hazard ratio for IUD expulsion				
25	By ≤ or > 36 weeks postpartum	X		

IRD = incidence rate difference; IRR = incidence rate ratio; IUD = intrauterine device.

9.9.4.4.3 Comparing adjusted hazard ratios for uterine perforation and IUD expulsion among subsequent IUD insertions

Estimation of adjusted HRs associated with subsequent (i.e., not the first) IUD insertions was conducted for secondary objectives 18 and 26 in Section 7.2.

These analyses were conducted similarly to those described in Sections 9.9.4.4.1 and 9.9.4.4.2. Options to account for correlation within women with multiple IUD insertions were explored for use with models for subsequent insertions to account for the inclusion of multiple IUD insertions per woman. If correlation among insertions within a woman could not be adequately addressed, then descriptive analyses were conducted for assessment of subsequent IUD insertions within a woman.

Pooled analyses included all sites regardless of the number of subsequent IUD insertions at a site. Site-specific analyses were performed only if more than 20,000 subsequent IUD insertions were available for a site.

9.9.4.4.4 Assessing effect modification

Estimation of effect modification of the adjusted HRs was conducted for secondary objectives 28 to 31 in Section 7.2.

The crude and adjusted HRs were estimated as described in Sections 9.9.2.4.1 and 9.9.2.4.3 within each level of the potential modifier. Cohort(s) of interest for each objective are indicated by "X" in Table 11.

Table 11. Study cohorts relevant to effect modification objectives

Objective number	Brief description	Complete study population	Within 52 weeks postpartum and breastfeeding status available	IUD type available
Uterine perforation outcome				
28	Breastfeeding modifies the association of uterine perforation with early (≤ 14 weeks) vs. late (> 14 weeks) postpartum IUD insertion		X	
29	IUD type modifies the association of uterine perforation with breastfeeding		X	
30	IUD type modifies the association of IUD expulsion with breastfeeding		X	
31	IUD type modifies the association of uterine perforation with IUD insertion at different time periods postpartum			X
32	IUD type modifies the association of IUD expulsion with IUD insertion at different time periods postpartum			X

IUD = intrauterine device.

For objective 28, the Cox models included breastfeeding status, early (≤ 14 weeks) versus late (> 14 weeks) postpartum IUD insertion, and their interaction. The *P* value of the type 3 group test for statistical interaction was reported. For reporting purposes, the group of no breastfeeding and IUD insertion > 14 weeks postpartum was considered the referent, and HRs were reported for IUD insertion ≤ 14 weeks postpartum and breastfeeding, IUD insertion ≤ 14 weeks postpartum and no breastfeeding, and IUD insertion > 14 weeks postpartum and breastfeeding compared with the referent. The adjusted HR was obtained using the weighted Cox model (Section 9.9.2.4.3). One propensity score model (using these four categories) was developed. Balance on baseline covariates among the four categories in the weighted sample was assessed.

For objectives 29 to 32, the Cox models included the exposure of interest (breastfeeding status or postpartum category), the outcome of interest (uterine perforation or IUD expulsion), IUD type, and the interaction between exposure and IUD type. The *P* value of the type 3 group test for statistical interaction was reported. The HR for exposure of interest was reported for each level of IUD type. The adjusted HR was obtained using the weighted Cox model (Section 9.9.2.4.3). The weights were estimated using the same propensity score models developed for the exposure-outcome pairing (Table 6).

9.9.5 Amendments to statistical analysis plan

Two additional analyses were added as sensitivity analyses.

1. *Analysis using censoring date based on extended use of IUD expiration for objectives 1 and 2 (uterine perforation for breastfeeding status and postpartum timing)*

   In this sensitivity analysis, the adjusted HR was estimated using the perforation event and the person-time at risk based on the extended use IUD expiration date (extended duration of use plus 3 months, defined in Section 9.4.4) as one of the censoring dates. The same weights used for objectives 1 and 2 were used in this sensitivity analysis. Analyses were conducted using the first observed IUD insertions.

2. *Adjusted odds ratios for objectives 16 and 24 (uterine perforation and IUD expulsion for IUD type)*

   In this sensitivity analysis, the adjusted odds ratios and 95% CIs were estimated using weighted logistic regression analysis. Odds ratio was adjusted for possible confounding effect using overlap weighting. The same weights used for objectives 16 (uterine perforation) and 24 (IUD expulsion) were used for the weighted logistic regression models. The dependent variable of the logistic regression model was uterine perforation confirmed during the person-time at risk and IUD expulsion confirmed during the person-time at risk, respectively. Analysis were conducted using the first observed IUD insertions. Due to data source restrictions, analyses were conducted using the pooled data, not by data source.

After reviewing results of the planned analyses, the following post hoc analyses were conducted for uterine perforation and for IUD expulsion, to further understand the results:

1. *Crude incidence rate and cumulative incidence for uterine perforation and IUD expulsion by postpartum time of IUD insertion (5 categories)*
2. *Hazard ratios for postpartum time of IUD insertion (5 categories)*
3. *Crude incidence rate and cumulative incidence for uterine perforation by menorrhagia status among women without a delivery in the past 52 weeks*

4. *Hazard ratios for uterine perforation and IUD expulsion, by menorrhagia status among women without a delivery in the past 52 weeks*
5. *Crude incidence rate and cumulative incidence for uterine perforation and IUD expulsion for exposure categories among subsequent IUD insertions*
6. *Crude incidence rate and cumulative incidence for uterine perforation and IUD expulsion for combinations of exposures included in interaction analyses*

9.10 Quality control

Standard operating procedures at RTI-HS guided the conduct of the study. For data analyses at each site, the standard operating procedures for the site were used to ensure data quality and security. Specifically, these procedures included internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. Range checks and general frequency tables were produced such that missing values, outliers, and inappropriate or abnormal values were identified. All data were checked for duplicate records (e.g., two records for one individual or two records for one procedure on the same day). A record of data quality problems and resolutions was kept at each site conducting data analysis. All inconsistencies and data quality issues were documented. A second data analyst at each site reviewed all SAS and data extraction code before study completion to ensure that the data extractions and case identifications were accurate and complete.

To ensure consistency across study sites, information on methods and approaches to ascertain exposure and outcome information were shared. All key study documents, such as the statistical analysis plan, and study reports underwent quality-control review, senior scientific review, editorial review, and review by all site investigators.

Procedures were consistent with the FDA's *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data* [22] and the International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices (GPP)* [23]. The European Medicines Agency (EMA) *Guideline on Good Pharmacovigilance Practices (GVP), Module VIII – Post-Authorisation Safety Studies*, echoes this approach [24]. At RTI-HS, an independent Office of Quality Assurance performed audits and assessments of the RTI-HS activities that involved various aspects of the project, including but not limited to education and training documentation and IRB documentation. Such audits were conducted by the Office of Quality Assurance according to established criteria in standard operating procedures and other applicable procedures.

10. Results

Study results are presented in the following sections and illustrated with tables and figures that summarize important findings. More complete results may be found in analysis tables and figures provided in stand-alone documents (see list in Annex 1).

10.1 Participants

In Figure 3 are numbers contributed from each research site to the complete study population and exclusions to derive the three study populations described in Section 9.9.2.1.1: (a) the complete study population, (b) population with IUD type available, and (c) population with breastfeeding status available (and IUD insertion within 12 months postpartum).

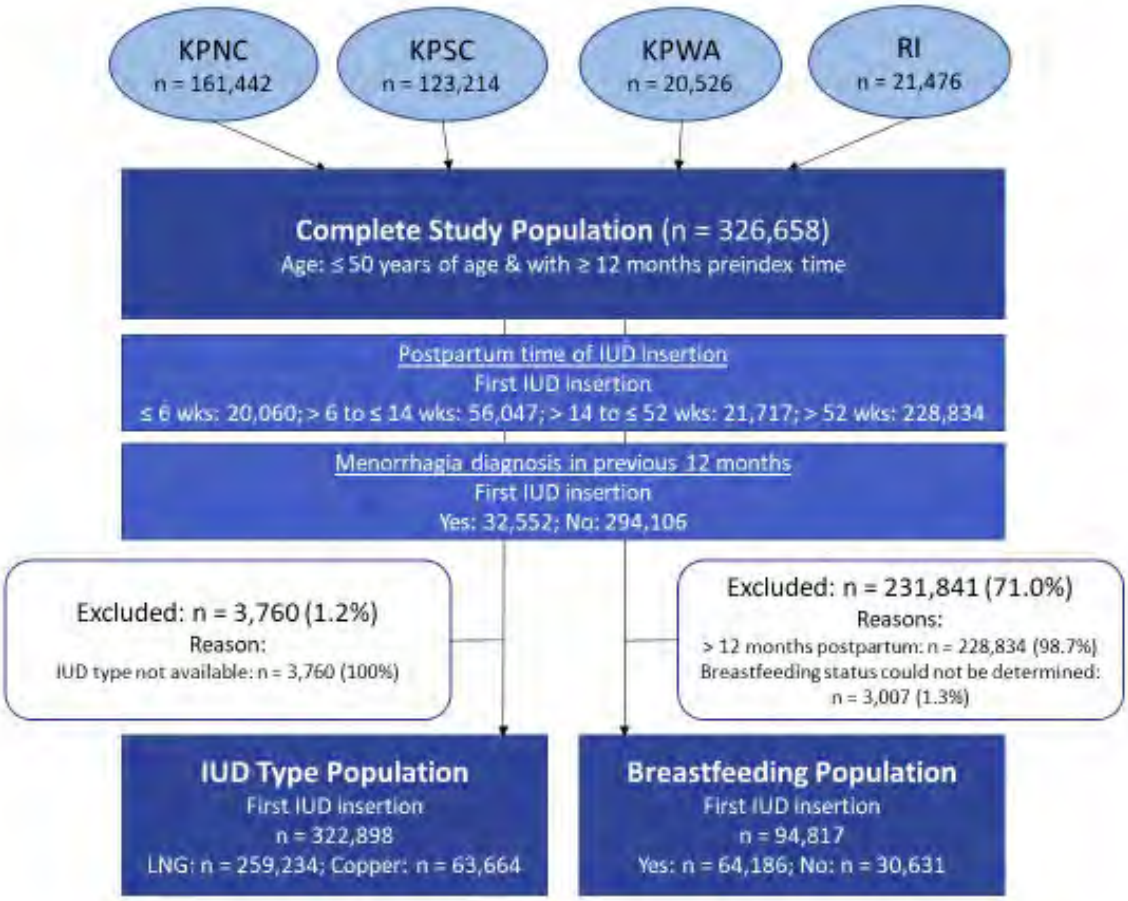


Figure 3: Diagram of study populations, exclusions, and number of first observed IUD insertions in exposure groups

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

The complete study population (first IUD insertion) included 326,658 insertions, and the population with IUD type available had 322,898 insertions—both populations had approximately 100,000 more than the 225,000 insertions anticipated (Section 9.7). Women with an IUD inserted within 52 weeks postpartum and with breastfeeding status available comprised 94,817 insertions, about 35,000 more than the 60,000 anticipated (Section 9.7).

- For the four-level postpartum timing of IUD insertion exposure (complete study population), we expected an allocation in the four postpartum groups of 5% for ≤ 6 weeks, 20% for > 6 to ≤ 14 weeks, 5% for > 14 to ≤ 52 weeks, and 70% for > 52 weeks; the actual proportions were 6.1%, 17.2%, 6.6%, and 70.1%, respectively.
- Menorrhagia as an exposure was also evaluated within the complete study population. Although we had no expected allocations for this exposure, we planned to conduct this analysis only if there were at least 20,000 IUD insertions with menorrhagia diagnosed in the previous 12 months (i.e., “recent”); 32,552 were identified for the first IUD insertions.

- For the IUD type comparison, we expected an allocation of 80% LNG and 20% copper; the actual proportions were 80.3% LNG and 19.7% copper for the first insertions.
- For breastfeeding status, we planned for 60% breastfeeding and 40% not breastfeeding at the time of IUD insertion. Among the first IUD insertions, the actual proportions were 67.7% breastfeeding and 32.3% not breastfeeding.

Thus, the study populations were larger than anticipated during planning and the proportions in the different exposure groups were very close to what was predicted.

10.2 Descriptive data

10.2.1 Characteristics of women for first observed IUD insertions

In Table 12 are summarized selected characteristics of the complete study population at the first IUD insertion, pooled and for each research site. The complete information on baseline characteristics for all three study populations, for first and subsequent IUD insertions, stratified by outcome, is in Analysis Tables 0.1.1 through 0.6.5. Approximately 19% of IUD insertions in the health care systems occurred in women who had previous exposure to an IUD within the data.

Table 12: Characteristics of the complete study population at the time of the first observed IUD insertions; pooled and by research site

	Pooled	KPNC	KPSC	KPWA	RI
Number of women	326,658	161,442	123,214	20,526	21,476
Person-years at risk	641,427	325,552	241,923	37,496	36,456
Characteristic					
Age (years)					
Mean (SD)	32.0 (8.30)	32.2 (8.33)	32.2 (8.26)	31.3 (8.22)	30.1 (8.03)
Categories, n (%)					
≤ 28 years	119,469 (36.6)	56,832 (35.2)	44,859 (36.4)	8,007 (39.0)	9,771 (45.5)
> 28 to ≤ 36 years	107,871 (33.0)	54,047 (33.5)	39,915 (32.4)	7,042 (34.3)	6,867 (32.0)
> 36 to ≤ 50 years	99,318 (30.4)	50,563 (31.3)	38,440 (31.2)	5,477 (26.7)	4,838 (22.5)
Race/ethnicity, n (%)					
Asian/Pacific Islander	38,911 (11.9)	26,216 (16.2)	9,998 (8.1)	2,122 (10.3)	575 (2.7)
Hispanic black	696 (0.2)	96 (0.1)	524 (0.4)	54 (0.3)	22 (0.1)
Hispanic other	56,180 (17.2)	33,967 (21.0)	21,284 (17.3)	716 (3.5)	213 (1.0)
Hispanic white	42,501 (13.0)	2,000 (1.2)	38,649 (31.4)	584 (2.8)	1,268 (5.9)
Non-Hispanic black	28,323 (8.7)	12,678 (7.9)	11,397 (9.2)	1,234 (6.0)	3,014 (14.0)
Non-Hispanic white	137,102 (42.0)	72,745 (45.1)	36,439 (29.6)	13,097 (63.8)	14,821 (69.0)
Other or multiple	16,357 (5.0)	12,249 (7.6)	2,913 (2.4)	492 (2.4)	703 (3.3)
Unknown	6,588 (2.0)	1,491 (0.9)	2,010 (1.6)	2,227 (10.8)	860 (4.0)
Recent smoker					
Yes, n (%)	32,623 (10.2)	14,929 (9.4)	11,288 (9.2)	1,680 (9.2)	4,726 (22.0)
No, n (%)	288,539 (89.8)	144,366 (90.6)	110,831 (90.8)	16,592 (90.8)	16,750 (78.0)
Unknown/missing, n	5,496	2,147	1,095	2,254	0

	Pooled	KPNC	KPSC	KPWA	RI
BMI (kg/m^2)					
Mean (SD)	28.5 (6.99)	28.0 (6.79)	28.9 (6.99)	28.0 (7.06)	30.0 (8.17)
Categories					
Underweight, n (%)	3,689 (1.1)	1,956 (1.2)	1,306 (1.1)	217 (1.1)	210 (1.2)
Normal weight, n (%)	113,675 (35.4)	61,437 (38.2)	39,041 (31.8)	8,010 (40.3)	5,187 (29.2)
Overweight, n (%)	96,181 (29.9)	47,887 (29.8)	37,631 (30.6)	5,638 (28.4)	5,025 (28.2)
Obese, n (%)	107,674 (33.5)	49,371 (30.7)	44,925 (36.6)	6,011 (30.2)	7,367 (41.4)
Missing, n	5,439	791	311	650	3,687
Dysmenorrhea diagnosis, n (%)					
Recent (≤ 12 months before index only)	10,893 (3.3)	3,861 (2.4)	5,651 (4.6)	863 (4.2)	518 (2.4)
Past (> 1 year before index only)	18,080 (5.5)	6,473 (4.0)	7,473 (6.1)	1,904 (9.3)	2,230 (10.4)
Diagnosis in recent & past periods	4,373 (1.3)	1,437 (0.9)	2,257 (1.8)	477 (2.3)	202 (0.9)
No diagnosis	293,312 (89.8)	149,671 (92.7)	107,833 (87.5)	17,282 (84.2)	18,526 (86.3)
Fibroids					
Yes, n (%)	17,416 (5.3)	7,742 (4.8)	8,096 (6.6)	1,271 (6.2)	307 (1.4)
Parity					
0, n (%)	61,920 (21.5)	36,814 (24.7)	18,980 (16.6)	3,973 (32.7)	2,153 (18.0)
> 0, n (%)	225,925 (78.5)	112,478 (75.3)	95,495 (83.4)	8,161 (67.3)	9,791 (82.0)
Missing, n	38,813	12,150	8,739	8,392	9,532
Cesarean delivery any time before the index date					
Yes, n (%)	54,295 (24.0)	25,233 (22.4)	22,939 (24.0)	2,295 (28.1)	3,828 (39.1)
No, n (%)	171,630 (76.0)	87,245 (77.6)	72,556 (76.0)	5,866 (71.9)	5,963 (60.9)
Parity of 0 or missing, n	100,733	48,964	27,719	12,365	11,685
Cesarean delivery for most recent delivery before the index date					
Yes, n (%)	23,245 (23.8)	10,081 (21.9)	10,638 (25.9)	1,402 (24.1)	1,124 (22.5)
No, n (%)	74,579 (76.2)	35,850 (78.1)	30,431 (74.1)	4,423 (75.9)	3,875 (77.5)
No delivery in past year, n	228,834	115,511	82,145	14,701	16,477
Concomitant gynecological procedure					
Yes[a], n (%)	26,234 (8.0)	13,494 (8.4)	10,770 (8.7)	1,275 (6.2)	695 (3.2)
Calendar year of IUD insertion, n (%)					
2001-2009	16,524 (5.1)	0	10,840 (8.8)	4,585 (22.3)	1,099 (5.1)
2010	31,563 (9.7)	18,206 (11.3)	11,032 (9.0)	1,847 (9.0)	478 (2.2)
2011	32,747 (10.0)	17,974 (11.1)	12,311 (10.0)	1,986 (9.7)	476 (2.2)
2012	36,584 (11.2)	19,911 (12.3)	13,728 (11.1)	2,111 (10.3)	834 (3.9)
2013	34,303 (10.5)	18,694 (11.6)	12,377 (10.0)	2,012 (9.8)	1,220 (5.7)
2014	33,946 (10.4)	18,769 (11.6)	11,699 (9.5)	1,963 (9.6)	1,515 (7.1)
2015	37,621 (11.5)	19,144 (11.9)	13,072 (10.6)	2,006 (9.8)	3,399 (15.8)
2016	41,302 (12.6)	20,242 (12.5)	14,894 (12.1)	1,773 (8.6)	4,393 (20.5)
2017	46,518 (14.2)	21,688 (13.4)	17,284 (14.0)	1,681 (8.2)	5,865 (27.3)
2018	15,550 (4.8)	6,814 (4.2)	5,977 (4.9)	562 (2.7)	2,197 (10.2)

	Pooled	KPNC	KPSC	KPWA	RI
Duration of look-back period (months)					
Mean (SD)	56.8 (42.33)	53.9 (28.66)	46.1 (28.72)	45.7 (31.09)	149.7 (77.15)
Min, max	12, 435	12, 112	12, 124	12, 148	12, 435

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

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

The mean age and frequency of age categories are relatively similar across all sites, with a slightly younger population represented in the RI data. Women receiving IUDs in the RI health care system are somewhat more obese than at the other sites. Across the four research sites, this is a diverse patient population in terms of race/ethnicity, with a higher proportion of blacks in the RI population than at the other sites, a higher proportion of Hispanic ethnicity at KPSC than the other sites, and a higher proportion of Asian/Pacific Islander at KPNC than at the other sites; non-Hispanic whites comprise the largest race/ethnicity groups at KPNC, KPWA, and RI. At KPNC, KPSC, and KPWA, members had to select both race and ethnicity to be included in Hispanic white or Hispanic black categories. If they selected only Hispanic and not race, then they were categorized as Hispanic other.

A larger proportion of women were recent smokers at RI than at the other sites. All three KP sites used data that queried smoking status during clinic visits. RI determined smoking status from NLP terms applied to clinical notes. Because virtually no information identified nonsmokers in the clinical notes, all patients at RI that were not classified as recent smokers were classified as nonsmokers, which accounts for the zero unknown/missing.

The prevalence of a dysmenorrhea diagnosis was similar across all research sites, and a smaller percentage of patients had a diagnosis of fibroids in the RI population. A larger proportion of nulliparous women received an IUD at KPWA and KPNC than at the other two sites. Compared with the KP sites, more women receiving an IUD insertion in the RI data had a history of cesarean section at any time prior to IUD insertion, but the sites were all quite similar in the proportion with a cesarean section at the most recent delivery. A lower proportion of patients had a concomitant procedure at the time of IUD insertion at RI than at the other sites. The average duration of the look-back period was longer at RI since the health information exchange has electronic health care records back to 1990, which could account for the larger proportion with a history of previous cesarean section.

The demographic characteristics of these women are representative of the regions represented by these health care systems.

10.2.2 Continuous enrollment for the complete study population

Duration of continuous enrollment is summarized in Table 13.

Table 13: Average length of continuous enrollment for the study population; pooled and by research site

	Pooled	KPNC	KPSC	KPWA	RI
Number of women	326,658	161,442	123,214	20,526	21,476
Characteristic					
Continuous enrollment (months)					
Mean (SD)	88.6 (46.33)	81.3 (32.52)	83.5 (37.06)	81.0 (43.03)	180.0 (78.09)
Median [Q1, Q3]	90.0 [52.7, 114.0]	89.0 [52.0, 114.0]	85.0 [49.3, 126.0]	74.0 [44.0, 119.0]	176.8 [123.2, 230.4]
Min, max	12.0, 438.2	12.0, 114.0	12.0, 126.0	13.0, 150.0	12.0, 438.2
Continuous enrollment on or before index date (months)					
Mean (SD)	51.9 (42.04)	44.1 (25.84)	46.1 (28.72)	45.7 (31.09)	149.7 (77.15)
Median [Q1, Q3]	39.9 [23.1, 67.4]	37.5 [22.4, 61.0]	38.2 [22.4, 63.3]	36.0 [21.5, 60.9]	145.9 [89.4, 201.6]
Min, max	12.0, 435.2	12.0, 112.0	12.0, 124.0	12.1, 148.0	12.0, 435.2
Continuous enrollment on or after index date (months)					
Mean (SD)	36.8 (29.54)	37.3 (28.20)	37.4 (30.60)	35.4 (32.87)	30.3 (29.08)
Median [Q1, Q3]	28.7 [11.9, 57.1]	30.7 [13.0, 58.2]	28.5 [11.6, 58.6]	24.3 [9.5, 52.8]	21.8 [9.6, 39.0]
Min, max	0.0, 209.6	0.0, 101.9	0.0, 114.0	0.1, 137.9	0.0, 209.6

KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; Q1 = lower quartile (i.e.; 25th percentile); Q3 = upper quartile (i.e.; 75th percentile); RI = Regenstrief Institute; SD = standard deviation.
Source: Analysis Tables 0.1.1 through 0.6.5.

Across all sites, median duration of continuous enrollment was 90.0 months (7.5 years), with a range of 74.0 to 176.8 months. RI has data back to 1990, which was included in the time before the index date. Median continuous enrollment after the index date across the research sites was 28.7 months, with a range of 21.8 to 30.7 months.

10.2.3 Exposure groups

Information on the size of the exposure groups is summarized in Table 14.

Table 14: Size of the exposure groups; pooled and by research site

	Pooled	KPNC	KPSC	KPWA	RI
Number of women	326,658	161,442	123,214	20,526	21,476
Person-years at risk	641,427	325,552	241,923	37,496	36,456
Characteristic					
Breastfeeding status (for those ≤ 52 weeks postpartum), n (%)					
Yes	64,186 (19.6)	34,357 (21.3)	23,679 (19.2)	3,964 (19.3)	2,186 (10.2)
No	30,631 (9.4)	10,996 (6.8)	17,027 (13.8)	875 (4.3)	1,733 (8.1)
Undetermined	3,007 (0.9)	578 (0.4)	363 (0.3)	986 (4.8)	1,080 (5.0)
No delivery in the past year	228,834 (70.1)	115,511 (71.5)	82,145 (66.7)	14,701 (71.6)	16,477 (76.7)
Postpartum time of IUD insertion, n (%)					
0 to 3 days	2,788 (0.9)	2,001 (1.2)	106 (0.1)	27 (0.1)	654 (3.0)
4 days to ≤ 6 weeks	17,272 (5.3)	10,615 (6.6)	4,818 (3.9)	747 (3.6)	1,092 (5.1)
≤ 6 weeks	20,060 (6.1)	12,616 (7.8)	4,924 (4.0)	774 (3.8)	1,746 (8.1)
> 6 to ≤ 14 weeks	56,047 (17.2)	24,259 (15.0)	25,880 (21.0)	3,682 (17.9)	2,226 (10.4)
> 14 to ≤ 52 weeks	21,717 (6.6)	9,056 (5.6)	10,265 (8.3)	1,369 (6.7)	1,027 (4.8)
> 52 weeks or no delivery	228,834 (70.1)	115,511 (71.5)	82,145 (66.7)	14,701 (71.6)	16,477 (76.7)

	Pooled	KPNC	KPSC	KPWA	RI
≤ 14 weeks	76,107 (23.3)	36,875 (22.8)	30,804 (25.0)	4,456 (21.7)	3,972 (18.5)
> 14 weeks or no delivery	250,551 (76.7)	124,567 (77.2)	92,410 (75.0)	16,070 (78.3)	17,504 (81.5)
≤ 36 weeks	91,869 (28.1)	43,175 (26.7)	38,495 (31.2)	5,483 (26.7)	4,716 (22.0)
> 36 weeks or no delivery	234,789 (71.9)	118,267 (73.3)	84,719 (68.8)	15,043 (73.3)	16,760 (78.0)
Menorrhagia, n (%) – complete study population					
≤ 12 months before insertion	32,552 (10.0)	13,593 (8.4)	15,727 (12.8)	2,027 (9.9)	1,205 (5.6)
> 12 months or no diagnosis	294,106 (90.0)	147,849 (91.6)	107,487 (87.2)	18,499 (90.1)	20,271 (94.4)
Menorrhagia, n (%) – population > 52 weeks postpartum					
≤ 12 months before insertion	31,600 (9.7)	13,204 (8.2)	15,297 (12.4)	1,961 (9.6)	1,138 (5.3)
> 12 months or no diagnosis	197,234 (60.4)	102,307 (63.4)	66,848 (54.3)	12,740 (62.1)	15,339 (71.4)
≤ 52 weeks postpartum	97,824 (29.9)	45,931 (28.5)	41,069 (33.3)	5,825 (28.4)	4,999 (23.3)
IUD type, n (%)[a]					
LNG-IUD	259,234 (79.4)	—	—	—	—
Copper IUD	63,664 (19.5)	—	—	—	—
Unknown	3,760 (1.2)	—	—	—	—

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

[a] Site-specific results are not presented in keeping with Data Use Agreements with Kaiser Permanente research sites.

Source: Analysis Tables 0.1.1 through 0.6.5.

Nearly 95,000 women across all sites had an IUD insertion within 52 weeks after delivery and had information in their record that allowed breastfeeding status at the time of IUD insertion to be determined. Of these, approximately twice as many were determined to be breastfeeding at the time of IUD insertion than not breastfeeding. The majority of women in the study (n = 228,834) had an IUD placement more than 52 weeks postpartum or no evidence of a delivery in their medical record, and this group is included in the referent population in the different postpartum exposure categories. For menorrhagia, at the time of the first identified IUD insertion, 10% of women had a menorrhagia diagnosis within 12 months before IUD insertion (range across sites, 5.6% to 12.8%). Approximately 79% of the first identified IUD insertions were LNG-releasing IUDs; 20% were copper IUDs; and for about 1%, IUD type was not indicated.

10.2.4 Censoring

The reasons for censoring pooled across all sites and for each site are in Table 15 and Table 16. Table 15 includes the information for censoring when labeled IUD duration was used, and Table 16 includes the same information for censoring when the extended duration for IUD use was used as a censoring event.

Table 15: Percentages of outcomes and censoring events; pooled and by site, first observed IUD insertions, complete study population; IUD labeled duration of use

Censoring event	Pooled (%)	KPNC (%)	KPSC (%)	KPWA (%)	RI (%)
Uterine perforation[a]	0.3	0.3	0.3	0.3	0.4
IUD expulsion[a]	2.7	3.1	2.6	2.1	1.4
Both perforation and expulsion[a]	0.0	0.0	0.0	0.0	0.0
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 (labeled, single reason)	4.5	4.8	4.1	4.4	3.7
Death (single reason)	0.1	0.1	0.1	0.0	0.1
End of enrollment/follow-up (single reason)	25.6	23.7	26.1	43.6	20.2
End of study period (single reason)	32.0	32.8	31.2	16.6	45.2
Other multiple reasons recorded on the censoring date	0.9	1.0	0.7	0.4	1.4
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] May have had a censoring event(s) in addition to uterine perforation and/or IUD expulsion recorded on the same date.

Table 16: Percentages of outcomes and censoring events; pooled and by site, first observed IUD insertions, complete study population; IUD extended duration of use

Censoring event	Pooled (%)	KPNC (%)	KPSC (%)	KPWA (%)	RI (%)
Uterine perforation[a]	0.3	0.3	0.3	0.3	0.4
IUD expulsion[a]	2.7	3.1	2.6	2.1	1.4
Both perforation and expulsion[a]	0.0	0.0	0.0	0.0	0.0
Removal of IUD (single reason)	25.6	26.7	25.2	24.0	21.5
Subsequent IUD insertion (single reason)	1.4	0.8	2.0	2.0	2.3
Both removal and subsequent insertion	6.6	7.3	6.7	6.0	1.7
Pregnancy (single reason)	1.3	0.9	1.6	1.6	1.7
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	0.4
IUD expiration (extended duration of use, single reason)	0.7	0.5	0.7	0.9	1.4
Death (single reason)	0.1	0.1	0.1	0.1	0.1
End of enrollment/follow-up (single reason)	25.9	23.9	26.4	44.3	20.5
End of study period (single reason)	33.8	35.0	32.6	17.6	46.4
Other multiple reasons recorded on the censoring date	0.9	1.0	0.7	0.4	1.4
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] May have had a censoring event(s) in addition to uterine perforation and/or IUD expulsion recorded on the same date.

In the study population pooled over sites, the proportion of censoring that occurred because of IUD expiration was 4.5% when the labeled duration was used and 0.7% when IUD use was extended 2 years beyond the labeled duration. Removal of IUD, subsequent IUD insertion, removal and subsequent insertion, end of enrollment/follow-up, and end of study period were the censoring events that largely accounted for the difference when IUD expiration was extended.

10.2.5 Complete versus partial uterine perforations and IUD expulsions

Both complete and partial perforations and expulsions were counted as an outcome in these analyses. This was thought to be the most conservative approach to quantifying incidence rates for the purpose of these safety outcomes. However, with the recognition that a partially expelled IUD might still provide effective contraception and a partial perforation (e.g., arm of the IUD embedded in the myometrium) might still be able to be removed by pulling on the strings, the partial outcomes might have a different safety profile. Therefore, the sites reviewed the records and provided an assessment regarding complete versus partial perforation and expulsion, whenever possible. In Table 17 is a summary of the proportion of these outcomes that were complete, partial, or unable to be determined and the evaluator's certainty about these classifications for uterine perforation.

Table 17: Proportion of complete and partial outcomes; pooled and by site, first observed IUD insertions, complete study population

	Pooled		KPNC		KPSC		KPWA		RI	
	N	%	N	%	N	%	N	%	N	%
Uterine perforation	1,008	100.0	529	100.0	324	100.0	64	100.0	91	100.0
Complete perforation										
Certain	515	51.1	230	43.5	206	63.6	39	60.9	40	44.0
Possible	1	0.1	0	0.0	1	0.3	0	0.0	0	0.0
Partial perforation										
Certain	305	30.3	175	33.1	80	24.7	15	23.4	35	38.5
Possible	183	18.2	124	23.4	37	11.4	10	15.6	12	13.2
Unable to determine if perforation was partial or complete										
Certain	4	0.4	0	0.0	0	0.0	0	0.0	4	4.4
Possible	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
IUD expulsion	5,471	100.0	5,035	100.0	-	-	436	100.0	-	-
Complete expulsion	2,616	47.8	2,496	49.6	-	-	120	27.5	-	-
Partial expulsion	2,480	45.3	2,164	43.0	-	-	316	72.5	-	-
Unable to determine if expulsion was partial or complete	375	6.9	375	7.4	-	-	0	0.0	-	-
Missing	3,472		0		3,172		0		300	

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

Across all sites, the proportion of uterine perforations that were judged to be complete was 51% (ranged from 43.5 to 63.6% across sites), and the proportion of these that were considered certain complete perforations was > 99%. There was less certainty about the diagnosis of partial perforation, with about 30% of the perforations determined to be a certain partial perforation and 18% a possible partial perforation. Very few uterine perforations were unable to be classified as complete or partial given the ability to assign certainty.

Not all sites were able to provide this information for IUD expulsions, but for those that were able to provide the information, about 48% of the expulsions were considered to be complete, 45% partial, and 7% were unable to be determined. We did not include a classification of certainty for IUD expulsion.

10.2.6 Evaluation of change from ICD-9 to ICD-10 codes on outcomes

Algorithms for the outcome variables uterine perforation and IUD expulsion were validated in these four data sources prior to use of 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 one of these outcomes was reviewed prior to and after the implementation of ICD-10-CM coding to evaluate consistency over time. Those data are summarized in Table 18.

Table 18: Proportion of patients with an IUD who had a uterine perforation or IUD expulsion within the 12 months before and 12 months after implementation of ICD-10 coding

Site	12 months before ICD-10 implementation			12 months after ICD-10 implementation		
	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	4,442	6 (0.14%)	35 (0.79%)	4,313	5 (0.12%)	38 (0.88%)
RI	3,074	10 (0.33%)	19 (0.62%)	5,004	9 (0.18%)	25 (0.50%)

ICD-10 = International Classification of Diseases, 10th Revision; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute.
Source: Analysis Table 34.1.

In the pooled data, 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 are based on a small number of events. RI identified the majority of its cases from NLP (so there would be little impact of the ICD code change), and they reviewed the records of all potential cases to verify case status.

10.2.7 Propensity score models

Complete information on the variables contributing to the propensity scores, the absolute standardized differences before and after overlap weighting, and the standardized differences before and after weighting are in analysis figures and analysis tables provided in stand-alone documents (see list in Annex 1). Summarized in Table 19 and Table 20 are the variables included in the propensity score models for uterine perforation (Table 19) and IUD expulsion (Table 20).

Table 19: Variables included in propensity score models for the uterine perforation outcome, by exposure

Variable	Exposures				
	Postpartum	Breastfeeding	IUD type	Menorrhagia	Postpartum x breastfeeding
Study objective	2	1	16	19	28
Postpartum time[a] (4 categories, 14 week and 36 week dichotomous)	Exposure	Y	Y	Y	
Postpartum time (14-week cut point)					Exposure
Breastfeeding		Exposure	Y	Y	Exposure
IUD type	Y	Y	Exposure	Y	Y
Menorrhagia	Y	Y	Y	Exposure	Y
Age (tertiles)	Y	Y	Y		Y
Age (continuous)				Y	
Race/ethnicity	Y	Y	Y	Y	Y
Recent smoker	Y	Y	Y	Y	Y
Duration of look-back period (quartiles)	Y	Y	Y	Y	Y

Variable	Exposures				
	Postpartum	**Breastfeeding**	**IUD type**	**Menorrhagia**	**Postpartum x breastfeeding**
Calendar year of index date	Y	Y	Y	Y	Y
BMI (categorical)	Y	Y	Y	Y	Y
BMI (continuous)					
Dysmenorrhea	Y	Y	Y	Y	Y
Fibroids	Y	Y	Y	Y	Y
Parity (≤ 1, > 1, missing)	Y	Y			Y
Parity (0, > 0, missing)			Y	Y	
Cesarean delivery any time before index date		Y	Y	Y	Y
Cesarean delivery for most recent delivery		Y	Y	Y	
Concomitant gynecological procedures	Y	Y	Y	Y	Y
Any difficult insertion	Y	Y	Y	Y	Y
Annualized number of IUD insertions in previous year (quartiles)	Y	Y	Y	Y	Y
Live birth within past 52 weeks, most recent delivery		Y	Y	Y	Y
Research site	Y	Y	Y	Y	Y
Postpartum (4 categories) x site interaction		Y			
Age tertiles x site interaction	Y				
Age continuous x site interaction				Y	
Recent smoker x site interaction	Y				
Calendar year of index x site interaction	Y				Y
Parity (≤ 1, > 1, missing) x site interaction	Y				

BMI = body mass index; IUD = intrauterine device.
[a] The same covariates were used for all postpartum time definitions when they were the only exposure

Table 20: Variables included in propensity score models for the IUD expulsion outcome for each exposure

Variable	Exposures			
	Postpartum	**Breastfeeding**	**IUD type**	**Menorrhagia**
Objective	23	20	24	27
Postpartum time (4 categories, 14 week and 36 week dichotomous)	Exposure	Y	Y	Y
Breastfeeding		Exposure	Y	Y
IUD type	Y	Y	Exposure	Y
Menorrhagia	Y	Y	Y	Exposure
Age (tertiles)	Y	Y	Y	Y
Age (continuous)				
Race/ethnicity	Y	Y	Y	Y
Recent smoker				
Duration of look-back period (quartiles)				

Variable	Exposures			
	Postpartum	**Breastfeeding**	**IUD type**	**Menorrhagia**
Calendar year of index date	Y	Y	Y	Y
BMI (categorical)	Y	Y	Y	Y
BMI (continuous)				
Dysmenorrhea	Y	Y	Y	Y
Fibroids	Y	Y	Y	Y
Parity (≤ 1, > 1, missing)	Y	Y		
Parity (0, > 0, missing)			Y	Y
Cesarean delivery any time before index date			Y	
Cesarean delivery for most recent delivery				Y
Concomitant gynecological procedures	Y	Y	Y	Y
Any difficult insertion	Y	Y	Y	Y
Annualized number of IUD insertions in previous year (quartiles)	Y	Y	Y	Y
Live birth within past 52 weeks, most recent delivery		Y	Y	Y
Research site	Y	Y	Y	Y
Postpartum (4 categories) x site interaction		Y	Y	
Age tertiles x site interaction	Y			Y
Age continuous x site interaction				
Recent smoker x site interaction				
Calendar year of index x site interaction	Y			
Parity (≤ 1, > 1, missing) x site interaction	Y			

BMI = body mass index; IUD = intrauterine device.

In the description of the results in Sections 10.4 and 10.5, we describe the balance in the variables that were selected to be included in the propensity scores using the two criteria described in Section 9.9.2.4.2. First, a variable was included, if the crude HR was greater than 1.11 or less than 0.90. Second, additional confounders were selected for inclusion within propensity score models if at least a 10% change in the HR of the exposure-outcome relationship occurred when adjusting for that variable, including at least a 10% change in any level of a categorical exposure variable relative to the referent group. There was imbalance in some levels of variables not included in the propensity scores in both the pooled and research site-specific analyses. Only imbalance after overlap weighting in variables included in the propensity scores is described in the results below, for both pooled and site-specific samples. However, the imbalance in all variables (whether or not included in the propensity scores) can be seen in the figures and tables with the content description in the List of Results Tables and Figures: for figures, “Standardized differences in the unweighted and weighted samples,” and for tables, “Baseline characteristics and absolute standardized differences after overlap weighting.”

10.3 Outcome data

The main results are focused on the first recorded IUD insertion within the study period. Results for subsequent insertions (objectives 18 and 26) are described in Sections 10.5.12 and 10.5.13.

10.4 Main results

10.4.1 Primary objective 1 (and objective 5): breastfeeding and uterine perforation–first observed IUD insertions

10.4.1.1 Uterine perforation and breastfeeding incidence–first observed IUD insertions (objective 5)

Objective 5: To estimate the incidence rate and cumulative incidence of uterine perforation among women who were within 52 weeks postpartum and were or were not breastfeeding at the time of IUD insertion

The crude incidence rate and 1- and 5-year cumulative incidence for uterine perforation by breastfeeding status among women who were within 52 weeks of delivery at the time of IUD insertion are in Table 21. The cumulative incidence of uterine perforation over follow-up time stratified by breastfeeding status at the time of IUD insertion is presented in Figure 4.

Table 21: Crude incidence rate (per 1,000 person-years) and cumulative incidence of uterine perforation at 1 year and 5 years, first observed IUD insertions stratified by breastfeeding status among women within 52 weeks postpartum; pooled and by research site

Research site and breastfeeding status	No. of insertions	Person-years	No. of events	Crude incidence rate (95% CI)	Crude cumulative incidence, 1 year (95% CI), %	Crude cumulative incidence, 5 years (95% CI), %
Pooled						
Breastfeeding	64,186	123,902.8	526	4.25 (3.89, 4.62)	0.60 (0.54, 0.67)	1.61 (1.43, 1.81)
Not breastfeeding	30,631	58,835.6	147	2.50 (2.11, 2.94)	0.35 (0.29, 0.43)	0.88 (0.71, 1.08)
Undetermined	3,007	5,685.1	26	4.57 (2.99, 6.70)	0.78 (0.50, 1.23)	1.36 (0.86, 2.16)
KPNC						
Breastfeeding	34,357	66,888.5	302	4.51 (4.02, 5.05)	0.60 (0.52, 0.70)	1.81 (1.55, 2.11)
Not breastfeeding	10,996	20,500.0	50	2.44 (1.81, 3.22)	0.32 (0.22, 0.45)	0.82 (0.58, 1.16)
Undetermined	578	986.8	4	4.05 (1.10, 10.38)	0.61 (0.20, 1.90)	0.98 (0.35, 2.72)
KPSC						
Breastfeeding	23,679	45,533.8	161	3.54 (3.01, 4.13)	0.54 (0.45, 0.65)	1.22 (0.99, 1.52)
Not breastfeeding	17,027	32,937.2	81	2.46 (1.95, 3.06)	0.38 (0.29, 0.50)	0.87 (0.65, 1.15)
Undetermined	363	736.5	3	4.07 (0.84, 11.90)	1.12 (0.36, 3.47)	1.12 (0.36, 3.47)
KPWA						
Breastfeeding	3,964	7,296.9	37	5.07 (3.57, 6.99)	0.73 (0.50, 1.08)	1.51 (1.04, 2.20)
Not breastfeeding	875	1,544.8	1	0.65 (0.02, 3.61)	0.12 (0.02, 0.84)	0.12 (0.02, 0.84)
Undetermined	986	1,404.6	5	3.56 (1.16, 8.31)	0.47 (0.15, 1.46)	1.06 (0.41, 2.71)
RI						
Breastfeeding	2,186	4,183.5	26	6.21 (4.06, 9.11)	0.90 (0.55, 1.48)	2.66 (1.65, 4.29)
Not breastfeeding	1,733	3,853.6	15	3.89 (2.18, 6.42)	0.37 (0.15, 0.89)	1.54 (0.88, 2.69)
Undetermined	1,080	2,557.3	14	5.47 (2.99, 9.19)	1.03 (0.55, 1.91)	1.80 (0.96, 3.37)

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

Source: Analysis Tables 3.1 to 3.5.

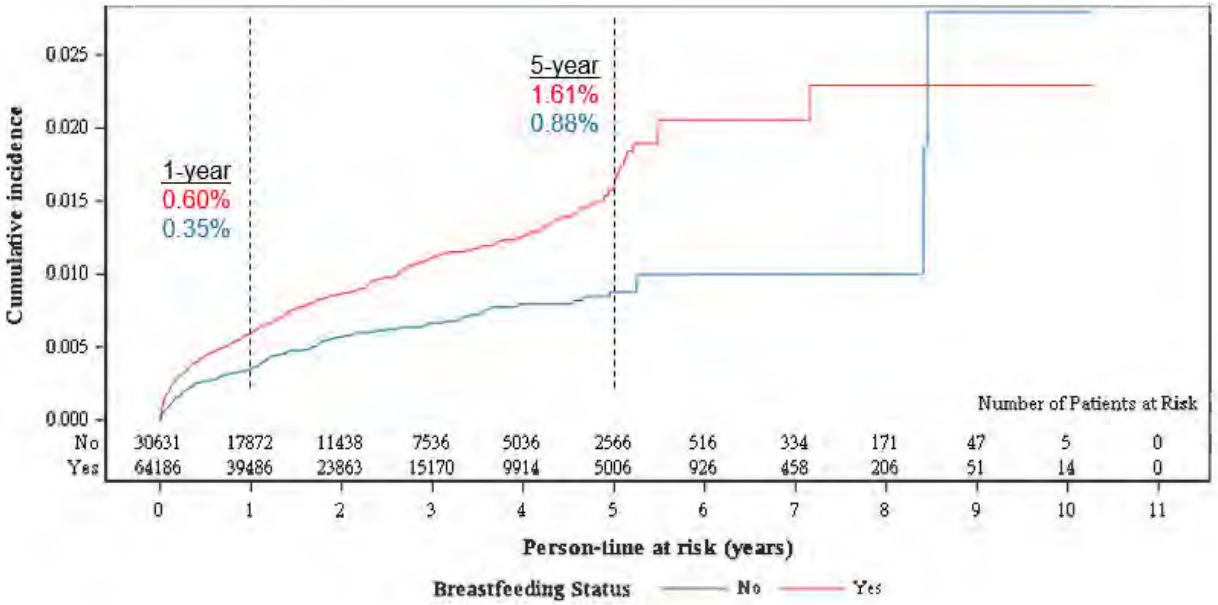


Figure 4: Crude cumulative incidence of uterine perforation by breastfeeding status; pooled study population (sources: data from Analysis Tables 3.1 and Analysis Figure 5.1)

The crude incidence rates and cumulative incidence at 1 and 5 years for uterine perforation are about 2 times higher among women who were breastfeeding at the time of IUD insertion (versus not breastfeeding), overall and across most research sites. At KPWA, the crude incidence for uterine perforation among those who were breastfeeding was about 8 times higher than that for those who were not breastfeeding. Uterine perforation among those with undetermined breastfeeding status is higher than that among those not breastfeeding overall and across all sites, although the CIs are wide at each site, indicating a lot of variability and small numbers of events. The cumulative incidence curves displayed in Figure 4 separate immediately after insertion; the curve for those who were breastfeeding is higher than the one for those not breastfeeding through 8 years of follow-up when very few women contributed to these estimates. Also, in Figure 4 and other cumulative incidence figures, an increase in the number of uterine perforations occurs at approximately 5 years after IUD insertion, which likely reflects uterine perforations that were recognized when women returned to have the IUD removed for those IUDs with a 5-year expiration.

10.4.1.2 Uterine perforation and breastfeeding risk–first observed IUD insertions (primary objective 1)

Objective 1: To evaluate whether the risk of uterine perforation among women who were breastfeeding at the time of first observed IUD insertion differs from the risk of uterine perforation among women who were not breastfeeding at the time of first observed IUD insertion

The crude and propensity score–adjusted HRs for breastfeeding status and uterine perforation for first IUD insertion are in Analysis Table 1.1, pooled and by research site. The pooled data are displayed in Figure 5. A sensitivity analysis to evaluate whether the association between breastfeeding status and uterine perforation differed across research sites was done by estimating the adjusted HR from a Cox model including exposure, site, site-by-exposure statistical interaction (type 3 group test for statistical interaction), and listed baseline covariates (Analysis Table 1.4). Because current clinical practice is to use IUDs for a longer period than the initial labeled time, we included a sensitivity analysis that used censoring based on extended IUD use (described in

Sections 9.4.4 and 9.9.5). The results of these two approaches to censoring are shown in Figure 5a and Figure 5b.

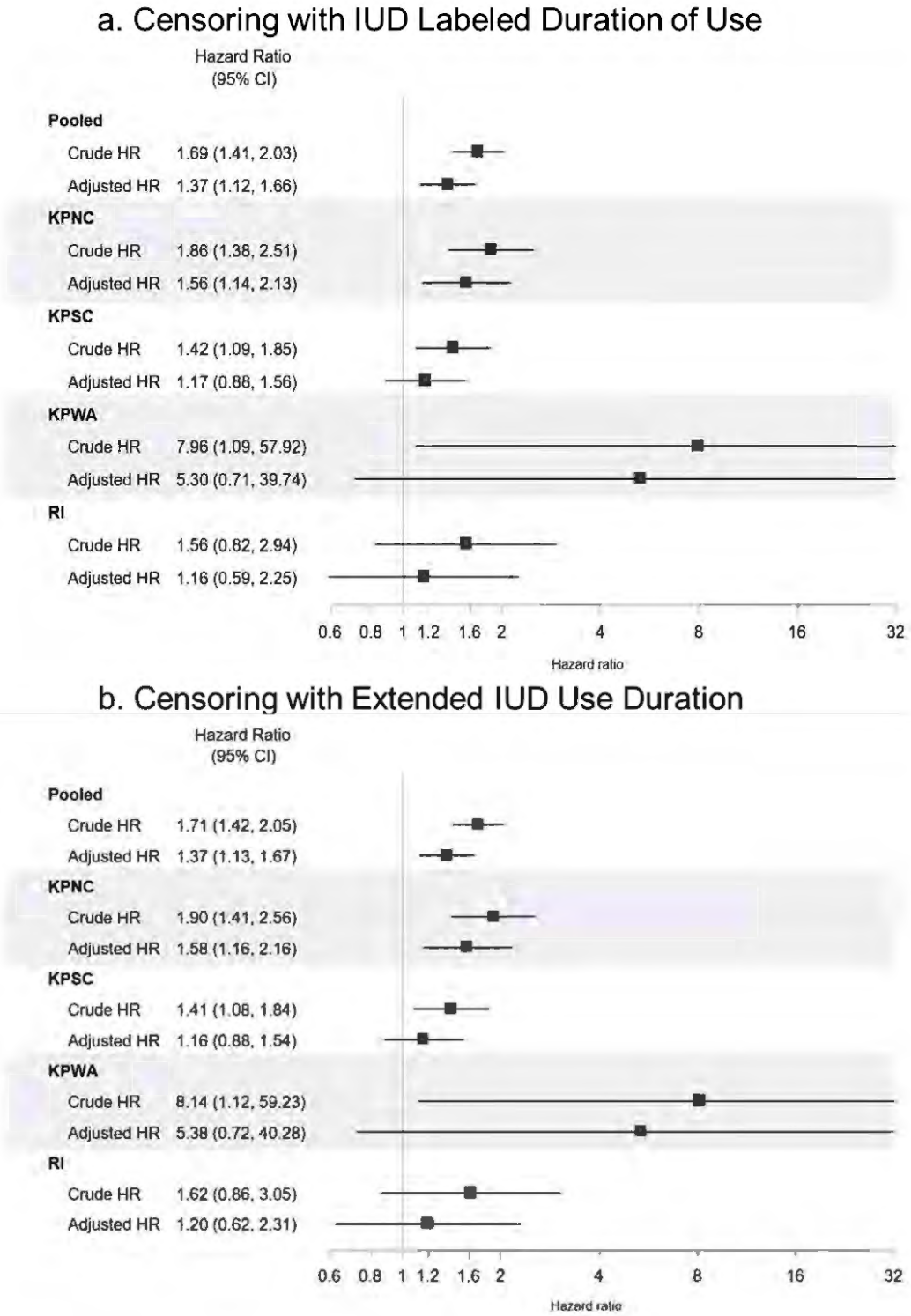


Figure 5: Crude and propensity score–adjusted hazard ratios of uterine perforation for women breastfeeding at the time of IUD insertion compared with women who were not breastfeeding at time of IUD insertion, pooled and by research site; population of women giving birth within the past 52 weeks, first observed IUD insertions; (a) censored at IUD labeled expiration duration; (b) censored at an extended IUD use duration (source: data from Analysis Tables 1.1 and 1.5)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.

Only those women who had given birth in the previous 52 weeks and had breastfeeding status “yes” or “no” were included in this analysis. The proportional hazards assumption was satisfied through 5 years after insertion. Standardized differences prior to confounding adjustment were substantial (pooled: Analysis Table 1.2.1; by site: Analysis Tables 1.2.2-1.2.5). After propensity score weighting using initial propensity score models, all levels of variables had satisfactory balance in the pooled data (absolute standardized difference < 0.2), and most were satisfactory at all sites. The exceptions were recent smoker at KPWA, calendar year of index (2001-2009) at KPWA and RI, calendar year of index (2015) at RI, postpartum status ≤ 6 weeks at KPWA, and postpartum status > 14 to ≤ 52 weeks at KPWA and RI. An interaction term by site was included, after which all levels of variables had satisfactory balance in the pooled data and were either satisfactory or attenuated at each site (Analysis Tables 1.3.1-1.3.5 and Analysis Figures 1.1.1-1.1.5). The analysis that evaluated whether the association between breastfeeding status and uterine perforation differed across research sites with individual covariates (rather than propensity score) included addressing confounding; results are shown in Analysis Table 1.4, and the *P* value for the group test for site-by–breastfeeding status interaction was 0.3571.

In crude analyses, women who were breastfeeding at the time of IUD insertion were more likely to have uterine perforation than women who were not breastfeeding (HR, 1.69 for pooled data). After adjustment, women who were breastfeeding at the time of IUD insertion remained more likely to have uterine perforation than women who were not breastfeeding, but the estimate was attenuated (adjusted HR, 1.37 for pooled data). These HRs are consistent with the trends in crude incidence and cumulative incidence, with adjustment attenuating the HRs.

The patterns for each research site were generally consistent with the pooled results, with wider CIs around the point estimates at the sites with fewer insertions (see Section 10.4.1.1). The HR point estimate for KPWA was higher than for other sites. At this site, a higher proportion of women were categorized as breastfeeding versus not breastfeeding. An assessment to evaluate whether there was difference across sites in the association between breastfeeding status and uterine perforation was not significant (type 3 group test for interaction: *P* = 0.2971).

Adding an additional 2 years for the censoring event of IUD expiration resulted in an additional 8 perforations in the breastfeeding group (total 534) and 1 perforation in the not-breastfeeding group (total 148) pooled across all sites (Analysis Tables 1.1 and 1.5). Therefore, the HRs and 95% CIs are virtually identical to those in Figure 5a and Figure 5b.

10.4.2 Primary objective 2 (objective 4 portion): postpartum timing and uterine perforation–first observed IUD insertions

10.4.2.1 Postpartum timing and incidence of uterine perforation—first observed IUD insertions (objective 4: 4-category postpartum timing and additional 5-category postpartum timing analysis)

10.4.2.1.1 Postpartum timing and incidence of uterine perforation—first observed IUD insertions (objective 4: 4-category postpartum timing)

Objective 4: To estimate the incidence rate and cumulative incidence of uterine perforation among women using IUDs for the following categories:

- *≤ 6 weeks postpartum*
- *> 6 weeks and ≤ 14 weeks postpartum*

- *> 14 weeks and ≤ 52 weeks postpartum*
- *> 52 weeks postpartum, including women without recorded delivery within the past 52 weeks*

The crude incidence rate and 1- and 5-year cumulative incidence for uterine perforation by postpartum time of IUD insertion are shown in Table 22. Figure 6 is a graphic display of the cumulative incidence of uterine perforation over follow-up time stratified by postpartum time of IUD insertion.

Table 22: Crude incidence rate (per 1,000 person-years) and cumulative incidence of uterine perforation at 1 year and 5 years, first observed IUD insertions stratified by postpartum timing of IUD insertion; pooled and for each research site

Research site	Weeks postpartum	Number of insertions	Person-years	Number of events	Crude incidence rate[a] (95% CI)	Crude cumulative incidence, 1 year (95% CI), %	Crude cumulative incidence, 5 years (95% CI), %
Pooled	≤ 6	20,060	37,173.8	191	5.14 (4.44, 5.92)	0.70 (0.59, 0.84)	1.89 (1.55, 2.31)
	> 6 to ≤ 14	56,047	110,573.8	417	3.77 (3.42, 4.15)	0.54 (0.48, 0.61)	1.42 (1.25, 1.61)
	> 14 to ≤ 52	21,717	40,676.0	91	2.24 (1.80, 2.75)	0.33 (0.26, 0.43)	0.74 (0.57, 0.97)
	> 52 or no delivery	228,834	453,003.7	309	0.68 (0.61, 0.76)	0.07 (0.06, 0.08)	0.29 (0.26, 0.34)
KPNC	≤ 6	12,616	23,091.8	122	5.28 (4.39, 6.31)	0.68 (0.54, 0.86)	2.05 (1.59, 2.63)
	> 6 to ≤ 14	24,259	48,413.3	196	4.05 (3.50, 4.66)	0.54 (0.45, 0.66)	1.59 (1.32, 1.92)
	> 14 to ≤ 52	9,056	16,870.2	38	2.25 (1.59, 3.09)	0.31 (0.21, 0.46)	0.86 (0.57, 1.32)
	> 52 or no delivery	115,511	237,176.2	173	0.73 (0.62, 0.85)	0.07 (0.06, 0.09)	0.34 (0.29, 0.41)
KPSC	≤ 6	4,924	8,712.2	43	4.94 (3.57, 6.65)	0.76 (0.54, 1.07)	1.66 (0.99, 2.76)
	> 6 to ≤ 14	25,880	51,315.4	167	3.25 (2.78, 3.79)	0.50 (0.42, 0.61)	1.18 (0.97, 1.44)
	> 14 to ≤ 52	10,265	19,180.0	35	1.82 (1.27, 2.54)	0.30 (0.20, 0.44)	0.50 (0.35, 0.73)
	> 52 or no delivery	82,145	162,715.7	79	0.49 (0.38, 0.61)	0.06 (0.04, 0.08)	0.19 (0.14, 0.25)

Research site	Weeks postpartum	Number of insertions	Person-years	Number of events	Crude incidence rate[a] (95% CI)	Crude cumulative incidence, 1 year (95% CI), %	Crude cumulative incidence, 5 years (95% CI), %
KPWA	≤ 6	774	1,272.8	8	6.29 (2.71, 12.38)	0.87 (0.39, 1.95)	1.55 (0.73, 3.28)
	> 6 to ≤ 14	3,682	6,489.4	27	4.16 (2.74, 6.05)	0.58 (0.36, 0.92)	1.34 (0.85, 2.10)
	> 14 to ≤ 52	1,369	2,484.1	8	3.22 (1.39, 6.35)	0.48 (0.21, 1.06)	0.78 (0.38, 1.63)
	> 52 or no delivery	14,701	27,249.9	21	0.77 (0.48, 1.18)	0.07 (0.04, 0.14)	0.25 (0.13, 0.47)
RI	≤ 6	1,746	4,097.1	18	4.39 (2.60, 6.94)	0.63 (0.32, 1.21)	1.74 (1.04, 2.91)
	> 6 to ≤ 14	2,226	4,355.7	27	6.20 (4.09, 9.02)	0.86 (0.53, 1.41)	2.38 (1.47, 3.84)
	> 14 to ≤ 52	1,027	2,141.7	10	4.67 (2.24, 8.59)	0.68 (0.30, 1.50)	1.86 (0.89, 3.87)
	> 52 or no delivery	16,477	25,861.9	36	1.39 (0.97, 1.93)	0.14 (0.09, 0.21)	0.55 (0.34, 0.91)

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

[a] Per 1,000 person-years.

Source: Analysis Tables 3.1 to 3.5.

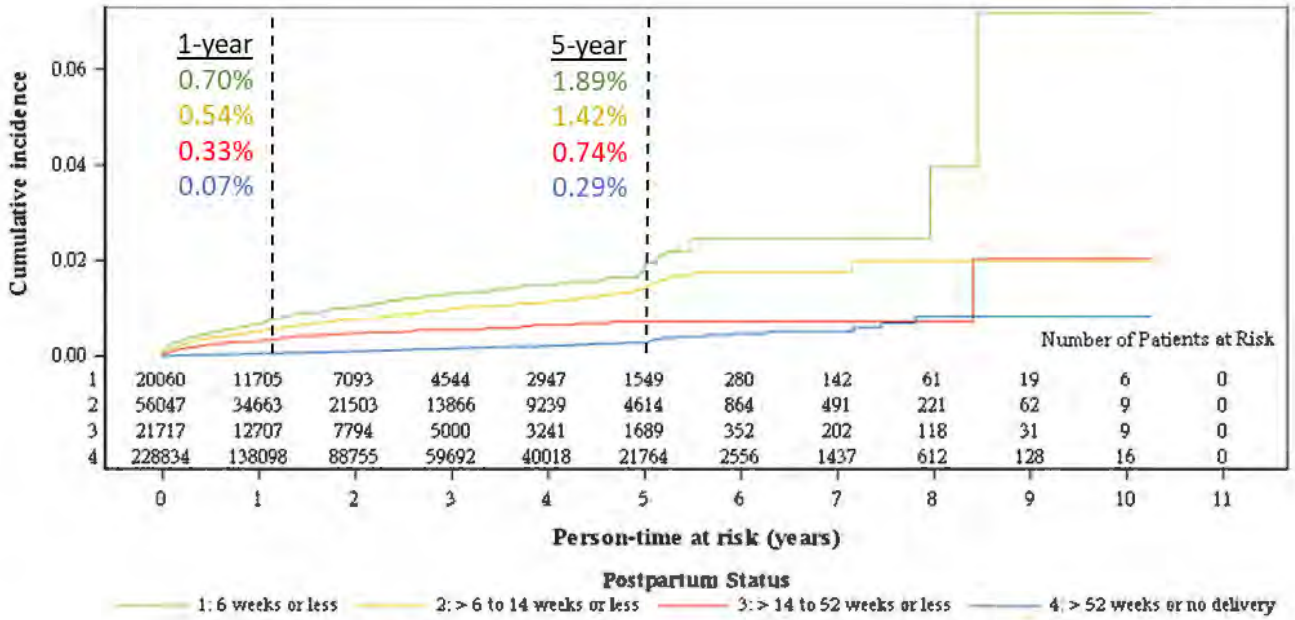


Figure 6: Crude cumulative incidence of uterine perforation by postpartum timing of IUD insertion (4 categories); pooled study population (source: data from Analysis Tables 3.1 and Figure 4.1)

IUD = intrauterine device.

The crude incidence rates and cumulative incidence at 1 and 5 years for uterine perforation are highest among those with IUD insertions ≤ 6 weeks postpartum for the pooled data and for each site except RI. For the postpartum timing of IUD insertions for the categories > 6 to ≤ 14 weeks, > 14 to ≤ 52 weeks, and > 52 weeks (or no recorded delivery), there is a trend toward lower incidence and lower cumulative incidence of uterine perforation with increasing postpartum time before IUD insertion in the pooled data and at each research site.

10.4.2.1.2 Postpartum timing and incidence of uterine perforation—first observed IUD insertions (additional analysis: 5-category postpartum timing)

Objective 4 (additional analysis): To estimate the incidence rate and cumulative incidence of uterine perforation among women using IUDs for the following categories:

- *≤ 3 days postpartum*
- *4 days to ≤ 6 weeks postpartum*
- *> 6 weeks to ≤ 14 weeks postpartum*
- *> 14 weeks to ≤ 52 weeks postpartum*
- *> 52 weeks postpartum, including women without recorded delivery within the past 52 weeks*

The crude incidence rate and 1- and 5-year cumulative incidence for uterine perforation by postpartum time of IUD insertion are shown in Table 23. Figure 7 is a graphic display of the cumulative incidence of uterine perforation over follow-up time stratified by postpartum time of IUD insertion.

Table 23: Crude incidence rate (per 1,000 person-years) and cumulative incidence of uterine perforation at 1 year and 5 years, first observed IUD insertions stratified by postpartum timing of IUD insertion; pooled and for each research site

Research site	Postpartum timing of IUD insertion	Number of insertions	Person-years	Number of events	Crude incidence rate[a] (95% CI)	Crude cumulative incidence, 1 year (95 CI), %	Crude cumulative incidence, 5 years (95 CI), %
Pooled	≤ 3 days	2,788	4,640.8	11	2.37 (1.18, 4.24)	0.22 (0.08, 0.60)	1.36 (0.62, 2.96)
	4 days to ≤ 6 weeks	17,272	32,533.0	180	5.53 (4.75, 6.40)	0.78 (0.65, 0.93)	1.98 (1.61, 2.43)
	> 6 to ≤ 14 weeks	56,047	110,573.8	417	3.77 (3.42, 4.15)	0.54 (0.48, 0.61)	1.42 (1.25, 1.61)
	> 14 to ≤ 52 weeks	21,717	40,676.0	91	2.24 (1.80, 2.75)	0.33 (0.26, 0.43)	0.74 (0.57, 0.97)
	> 52 weeks or no delivery	228,834	453,003.7	309	0.68 (0.61, 0.76)	0.07 (0.06, 0.08)	0.29 (0.26, 0.34)
KPNC	≤ 3 days	2,001	3,049.5	8	2.62 (1.13, 5.17)	0.27 (0.09, 0.83)	1.82 (0.71, 4.61)
	4 days to ≤ 6 weeks	10,615	20,042.3	114	5.69 (4.69, 6.83)	0.75 (0.59, 0.96)	2.10 (1.63, 2.71)
	> 6 to ≤ 14 weeks	24,259	48,413.3	196	4.05 (3.50, 4.66)	0.54 (0.45, 0.66)	1.59 (1.32, 1.92)
	> 14 to ≤ 52 weeks	9,056	16,870.2	38	2.25 (1.59, 3.09)	0.31 (0.21, 0.46)	0.86 (0.57, 1.32)
	> 52 weeks or no delivery	115,511	237,176.2	173	0.73 (0.62, 0.85)	0.07 (0.06, 0.09)	0.34 (0.29, 0.41)
KPSC	≤ 3 days	106	88.9	0	0.00 (0.00, 41.51)	0.00 (NE, NE)	NE
	4 days to ≤ 6 weeks	4,818	8,623.3	43	4.99 (3.61, 6.72)	0.77 (0.55, 1.09)	1.67 (1.01, 2.78)
	> 6 to ≤ 14 weeks	25,880	51,315.4	167	3.25 (2.78, 3.79)	0.50 (0.42, 0.61)	1.18 (0.97, 1.44)
	> 14 to ≤ 52 weeks	10,265	19,180.0	35	1.82 (1.27, 2.54)	0.30 (0.20, 0.44)	0.50 (0.35, 0.73)
	> 52 weeks or no delivery	82,145	162,715.7	79	0.49 (0.38, 0.61)	0.06 (0.04, 0.08)	0.19 (0.14, 0.25)

Research site	Postpartum timing of IUD insertion	Number of insertions	Person-years	Number of events	Crude incidence rate[a] (95% CI)	Crude cumulative incidence, 1 year (95 CI), %	Crude cumulative incidence, 5 years (95 CI), %
KPWA	≤ 3 days	27	34.1	1	29.31 (0.74, 163.32)	0.00 (NE, NE)	NE
	4 days to ≤ 6 weeks	747	1,238.7	7	5.65 (2.27, 11.64)	0.90 (0.40, 2.02)	1.23 (0.56, 2.69)
	> 6 to ≤ 14 weeks	3,682	6,489.4	27	4.16 (2.74, 6.05)	0.58 (0.36, 0.92)	1.34 (0.85, 2.10)
	> 14 to ≤ 52 weeks	1,369	2,484.1	8	3.22 (1.39, 6.35)	0.48 (0.21, 1.06)	0.78 (0.38, 1.63)
	> 52 weeks or no delivery	14,701	27,249.9	21	0.77 (0.48, 1.18)	0.07 (0.04, 0.14)	0.25 (0.13, 0.47)
RI	≤ 3 days	654	1,468.3	2	1.36 (0.16, 4.92)	0.16 (0.02, 1.10)	0.50 (0.11, 2.17)
	4 days to ≤ 6 weeks	1,092	2,628.8	16	6.09 (3.48, 9.88)	0.89 (0.44, 1.78)	2.43 (1.40, 4.20)
	> 6 to ≤ 14 weeks	2,226	4,355.7	27	6.20 (4.09, 9.02)	0.86 (0.53, 1.41)	2.38 (1.47, 3.84)
	> 14 to ≤ 52 weeks	1,027	2,141.7	10	4.67 (2.24, 8.59)	0.68 (0.30, 1.50)	1.86 (0.89, 3.87)
	> 52 weeks or no delivery	16,477	25,861.9	36	1.39 (0.97, 1.93)	0.14 (0.09, 0.21)	0.55 (0.34, 0.91)

CI = confidence interval; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; NE = not estimable; RI = Regenstrief Institute.

[a] Per 1,000 person-years.

Source: Additional Analysis Table 4.1

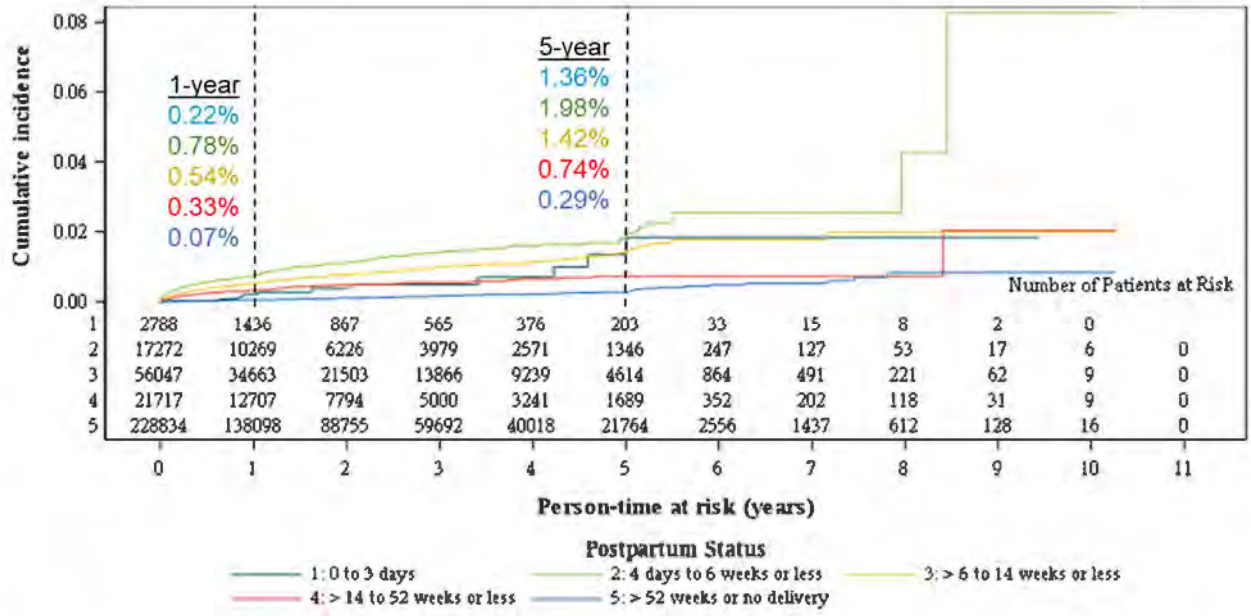


Figure 7: Crude cumulative incidence of uterine perforation by postpartum timing of IUD insertion (5 categories); pooled study population (source: data from Additional Analysis Table 4.1, Additional Analysis Figure 4.2.1)

IUD = intrauterine device.

The crude incidence rates and cumulative incidence at 1 and 5 years for uterine perforation are highest among those with IUD insertions 4 days to ≤ 6 weeks postpartum for the pooled data and for each site except the KPWA 5-year cumulative incidence estimate. For the postpartum timing of IUD insertions for > 6 to ≤ 14 weeks, > 14 to ≤ 52 weeks, and > 52 weeks (or no recorded delivery), there is a trend toward lower incidence and lower cumulative incidence of uterine perforation with increasing postpartum time before IUD insertion in the pooled data and at each research site. The incidence rates and cumulative incidence for the category of postpartum IUD insertion at ≤ 3 days are generally less than the rates for the category > 3 days to ≤ 6 weeks, except for the KPWA crude incidence rate, which was based on only 34 person-years of exposure and 1 uterine perforation.

10.4.2.2 Postpartum timing and uterine perforation risk—first observed IUD insertions (primary objective 2) and additional analysis (5-category postpartum timing)

10.4.2.2.1 Postpartum timing and uterine perforation risk—first observed IUD insertions (primary objective 2)

Objective 2: To evaluate whether the risk of uterine perforation among women who had a first observed IUD insertion within different time periods postpartum (i.e., ≤ 6 weeks, > 6 weeks and ≤ 14 weeks, > 14 weeks and ≤ 52 weeks) differs from the risk of uterine perforation among women who had their first observed IUD insertion more than 52 weeks postpartum, including women without a recorded delivery within the past 52 weeks

The crude, propensity score–adjusted, and fully adjusted ("fully" meaning adjusted for propensity score and breastfeeding status) HRs for the four-category postpartum timing and uterine perforation for the first postpartum IUD insertion are in Figure 8 and Figure 9, pooled and by research site. A

sensitivity analysis to evaluate whether the association between postpartum timing of IUD insertion and uterine perforation differed across research sites was done by estimating the adjusted HR from a Cox model including exposure, site, site-by-exposure statistical interaction (type 3 group test for statistical interaction), and listed baseline covariates (Analysis Table 2.4). Because current clinical practice is to use IUDs for a longer period than the initial labeled time, we included a sensitivity analysis for this analysis that included censoring based on extended IUD use (described in Sections 9.4.4 and 9.9.5). The results of these two approaches to censoring are in Figure 8a and Figure 8b.

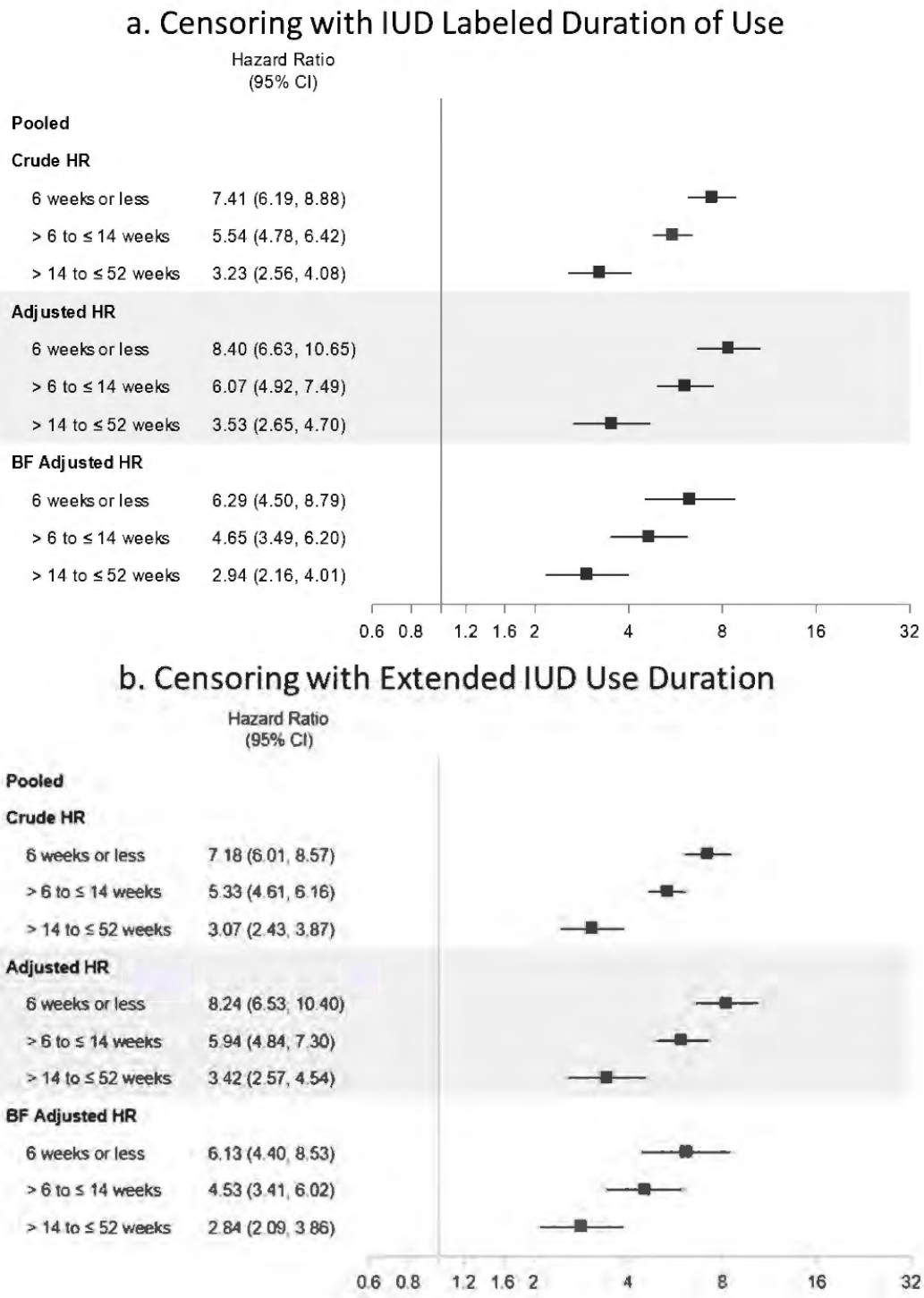


Figure 8: Crude, propensity score–adjusted, and fully adjusted hazard ratios for uterine perforation for three categories of postpartum timing at IUD insertion compared with those who were more than 52 weeks postpartum or with no recorded delivery; pooled complete study population, first observed IUD insertions; (a) censored at IUD labeled expiration; (b) censored at an extended IUD use (source: data from Analysis Tables 2.1 and 2.5)

Adjusted HR = adjusted for propensity scores; BF Adjusted HR or fully adjusted = adjusted for propensity scores and breastfeeding status; CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.

The complete study population was included in this analysis. The proportional hazards assumption was determined to be met based on visual inspection of the curves. Standardized differences prior to confounding adjustment were substantial (Analysis Table 2.2.1 and Analysis Figure 2.1.1 [pooled]; Analysis Tables 2.2.2-2.2.5 and Analysis Figures 2.1.2-2.1.5 [each research site]). After propensity score weighting, most of the variables included in the model had satisfactory balance (absolute standardized difference < 0.2) (Analysis Tables 2.3.1-2.3.5 and Analysis Figures 2.1.1-2.1.5). Among the variables included in the propensity scores, the exceptions were race/ethnicity Hispanic other (KPSC) and BMI missing (KPWA), both of which were marginally unbalanced. Breastfeeding could not be included in the propensity score model because in the category > 52-week postpartum, no woman was categorized as breastfeeding at the time of IUD insertion; therefore, breastfeeding status was included as a covariate separate from the propensity score model. The analysis that evaluated whether the association between postpartum timing of IUD insertion and uterine perforation differed across research sites with individual covariates (rather than propensity score) included addressing confounding; results are in Analysis Table 2.4, and the *P* value for the type 3 group test for site-by–postpartum timing interaction was 0.4126.

When compared with women with IUDs inserted more than 52 weeks postpartum (or with no delivery identified in the previous 52 weeks) (Figure 8), risk of uterine perforation appears to be graded, with the highest risk of uterine perforation in the women with an IUD inserted ≤ 6 weeks postpartum, lower risk in the group with IUD insertion > 6 but ≤ 14 weeks, and the lowest risk (among those with an IUD inserted within the first 52 weeks postpartum) in those with IUD insertions > 14 but ≤ 52 weeks postpartum. Adjusting for propensity score had minimal effect on the point estimates, and adjusting for breastfeeding in addition to propensity scores marginally attenuated the HRs.

Adding an additional 2 years to the censoring event of IUD expiration resulted in an additional 4 perforations in the group with IUD insertion ≤ 6 weeks postpartum (total 195), 5 additional in the group > 6 to ≤ 14 weeks (total 422), 0 additional in the group > 14 to ≤ 52 weeks (total 91), and 19 in the group > 52 weeks (total 328) pooled across all sites (Analysis Tables 2.1 and 2.5). Therefore, the HRs and CIs were very similar to those in Figure 8a and Figure 8b.

The patterns for each research site (Figure 9) were generally consistent, with a single exception—the HR point estimate for the category at RI ≤ 6 weeks postpartum was not higher than the second postpartum category (> 6 but ≤ 14 weeks). The assessment to evaluate whether there was difference across sites in the association between postpartum timing and uterine perforation was not significant (type 3 group test for interaction: $P = 0.4580$). These HRs are consistent with the trends in crude incidence and cumulative incidence. The data in Figure 9 used the labeled IUD expiration as a censoring event. Because of the smaller number of IUD insertions at KPWA and RI, the 95% CIs were wider than those for KPNC and KPSC.

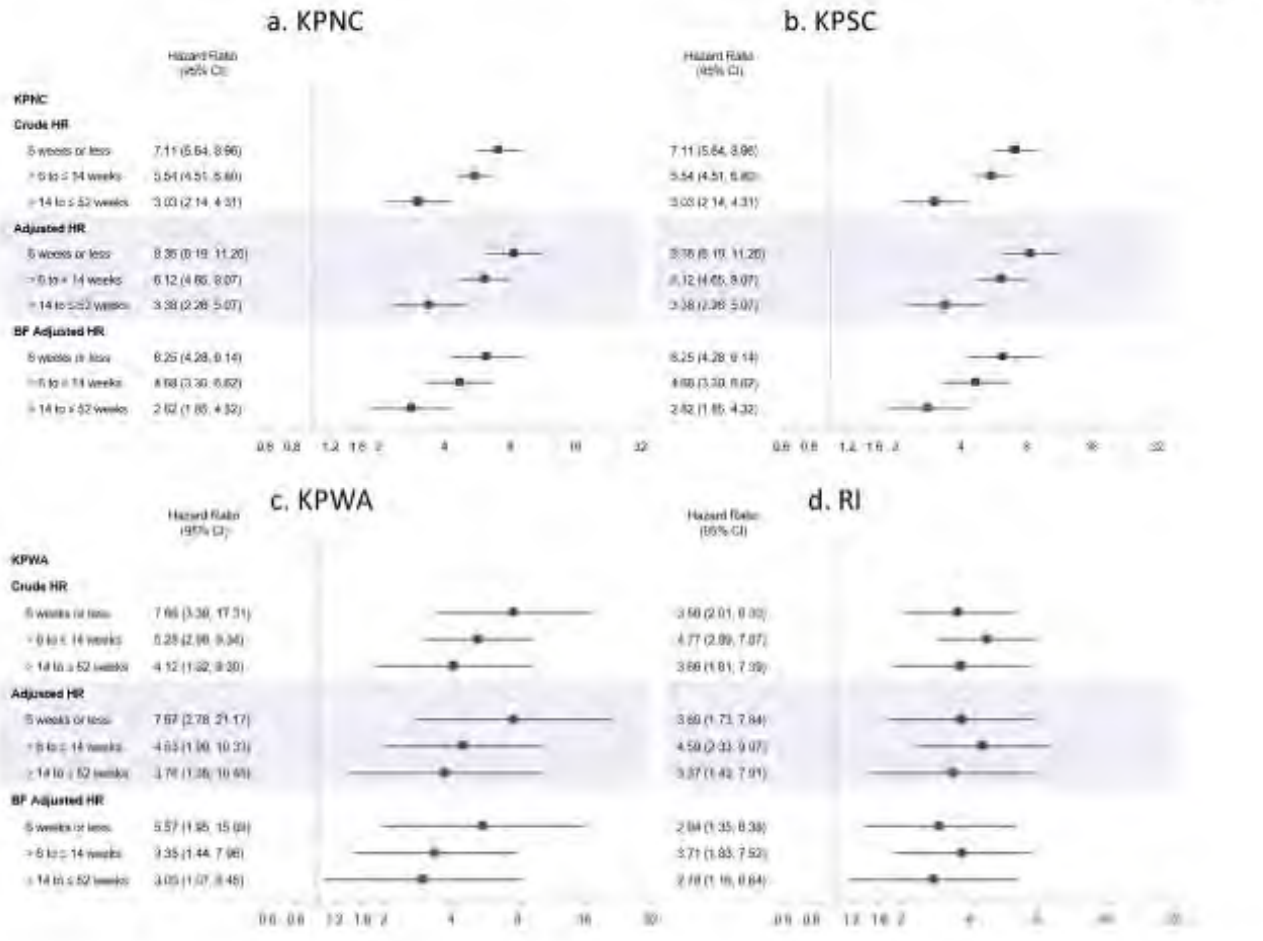


Figure 9: Crude, propensity score–adjusted, and fully adjusted (for propensity score and breastfeeding status) hazard ratios for uterine perforation for three categories of postpartum timing at IUD insertion compared with those who were more than 52 weeks postpartum or with no recorded delivery; first observed IUD insertions (a) KPNC, (b) KPSC, (c) KPWA, (d) RI (sources: data from Analysis Table 2.5)

Adjusted HR = adjusted for propensity scores; BF Adjusted HR or fully adjusted = adjusted for propensity scores and breastfeeding status; CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute.

10.4.2.2.2 Postpartum timing and uterine perforation risk—first observed IUD insertions (additional analysis: 5-category postpartum timing)

The crude, propensity score–adjusted, and fully adjusted HRs for the 5-category postpartum timing of IUD insertion with uterine perforation are shown in Figure 10.

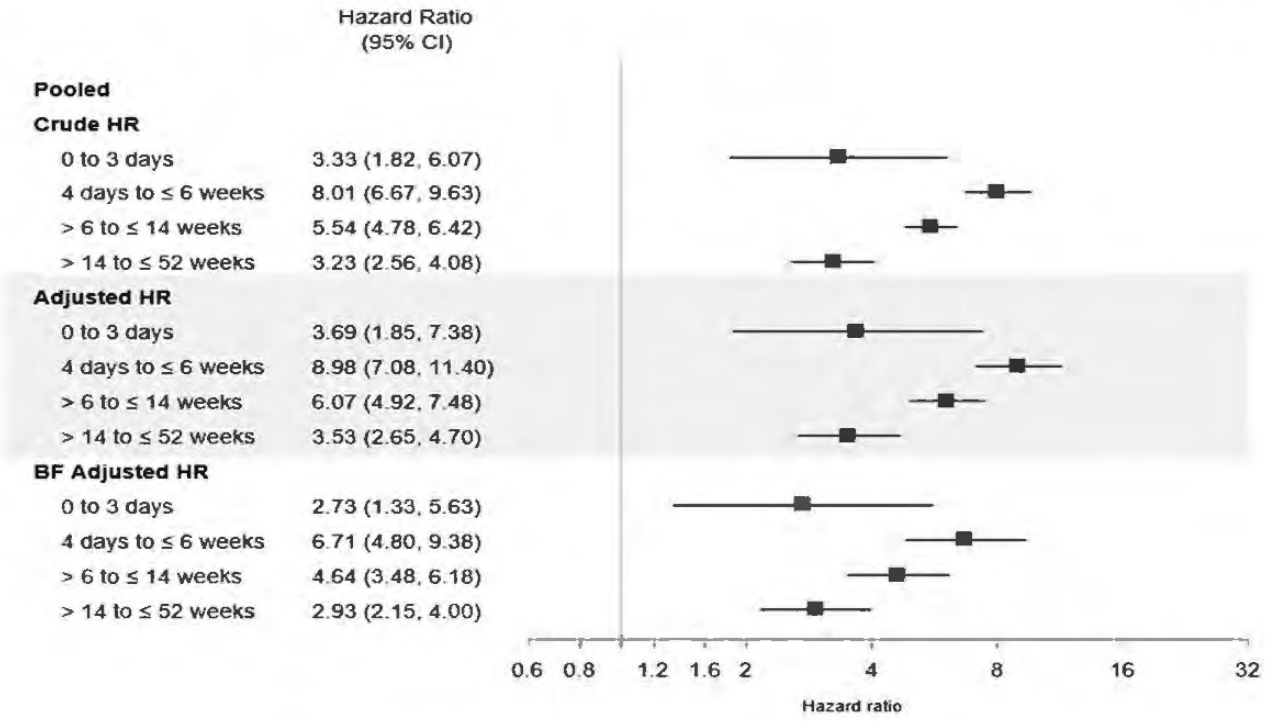


Figure 10: Crude, propensity score–adjusted, and fully adjusted hazard ratios for uterine perforation for four categories of postpartum timing at IUD insertion compared with those who were more than 52 weeks postpartum or with no recorded delivery; pooled complete study population, first observed IUD insertions (source: data from Additional Analysis Table 35.1)

Adjusted HR = adjusted for propensity scores; BF Adjusted HR or fully adjusted = adjusted for propensity scores and breastfeeding status; CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.

The complete study population was included in this analysis. The same propensity score weighting that was used for the 4-category postpartum timing analysis was used for this one. When compared with women with IUDs inserted more than 52 weeks postpartum (or with no delivery identified in the previous 52 weeks) (Figure 10), the earliest postpartum category (0-3 days postpartum) had a lower risk of uterine perforation than the category 4 days to ≤ 6 weeks, but after that time, risk of perforation appears to be a graded, with the highest risk in the women with an IUD inserted 4 days to ≤ 6 weeks postpartum, lower risk in the group with IUD insertion > 6 to ≤ 14 weeks, and a risk in those with IUD insertions > 14 to ≤ 52 weeks postpartum very similar to the group with IUD insertion 0 to 3 days postpartum. Adjusting for propensity score had minimal effect on the point estimates, and adjusting for breastfeeding in addition to propensity scores marginally attenuated the HRs.

10.5 Other analyses

10.5.1 Uterine perforation for women using IUDs—first observed IUD insertions (objective 3)

Objective 3: To estimate the incidence rate and cumulative incidence of uterine perforation among women using IUDs

The crude incidence rate and 1- and 5-year cumulative incidence for uterine perforation for the three study populations—complete, breastfeeding status available, IUD type available—are available in Table 24 and Figure 11.

Table 24: Crude incidence rates (per 1,000 person-years) and cumulative incidence of uterine perforation at 1 year and 5 years for first observed IUD insertions for the three study populations; pooled and by research site

Research site and study population	No. of inser-tions	Person-years	No. of events	Crude incidence rate (95% CI)	Crude cumulative incidence, 1 year (95% CI), %	Crude cumulative incidence, 5 years (95% CI), %
Pooled						
Complete study population	326,658	641,427.2	1,008	1.57 (1.48, 1.67)	0.21 (0.19, 0.23)	0.61 (0.56, 0.66)
Breastfeeding status available	94,817	182,738.4	673	3.68 (3.41, 3.97)	0.52 (0.47, 0.57)	1.37 (1.24, 1.52)
IUD type available	322,898	634,738.1	996	1.57 (1.47, 1.67)	0.21 (0.19, 0.22)	0.61 (0.56, 0.66)
KPNC[a]						
Complete study population	161,442	325,551.5	529	1.62 (1.49, 1.77)	0.20 (0.18, 0.23)	0.68 (0.61, 0.76)
Breastfeeding status available	45,353	87,388.5	352	4.03 (3.62, 4.47)	0.53 (0.47, 0.61)	1.58 (1.37, 1.82)
KPSC[a]						
Complete study population	123,214	241,923.2	324	1.34 (1.20, 1.49)	0.20 (0.17, 0.23)	0.48 (0.41, 0.55)
Breastfeeding status available	40,706	78,471.1	242	3.08 (2.71, 3.50)	0.48 (0.41, 0.56)	1.07 (0.90, 1.27)
KPWA[a]						
Complete study population	20,526	37,496.2	64	1.71 (1.31, 2.18)	0.22 (0.16, 0.30)	0.52 (0.38, 0.71)
Breastfeeding status available	4,839	8,841.7	38	4.30 (3.04, 5.90)	0.62 (0.43, 0.91)	1.27 (0.87, 1.84)
RI[a]						
Complete study population	21,476	36,456.3	91	2.50 (2.01, 3.06)	0.28 (0.21, 0.37)	0.99 (0.75, 1.32)
Breastfeeding status available	3,919	8,037.1	41	5.10 (3.66, 6.92)	0.66 (0.43, 1.02)	2.12 (1.47, 3.03)

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

[a] Site-specific results for the IUD type population are not presented at the request of Kaiser research sites.

Source: Analysis Tables 3.1 to 3.5.

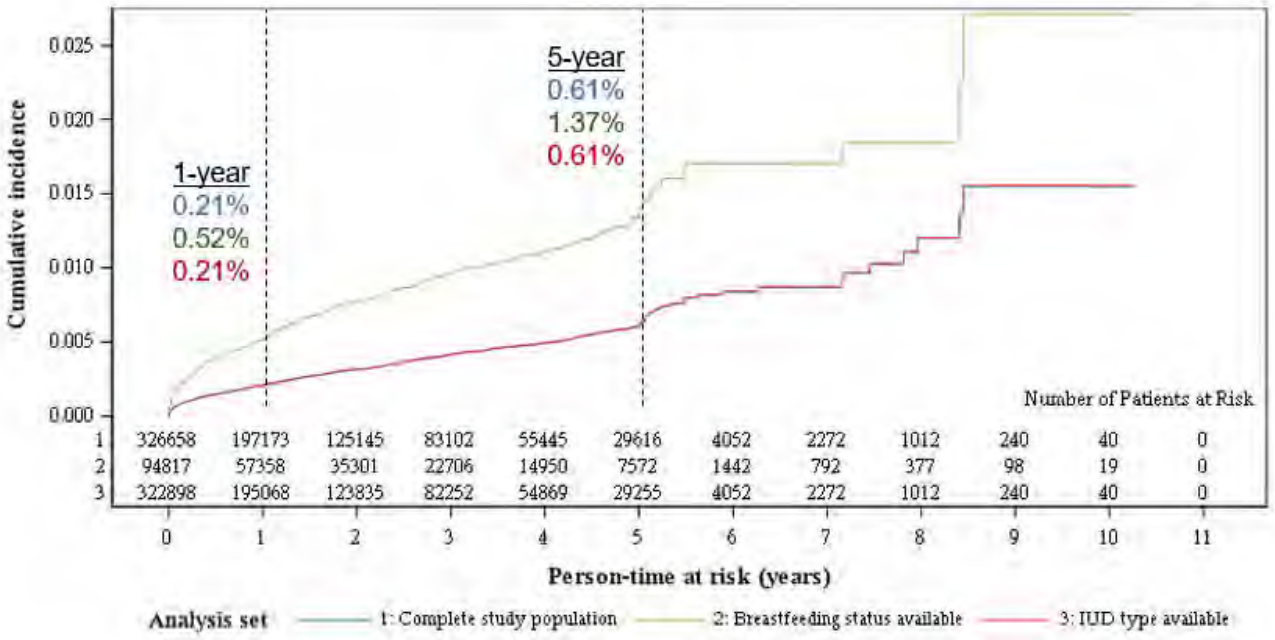


Figure 11: Crude cumulative incidence of uterine perforation pooled across sites for the three study populations: complete, breastfeeding status available, and IUD type available (source: data from Analysis Table 3.1, Analysis Figure 3.1)

IUD = intrauterine device.

The complete study population included 326,658 women with an IUD insertion with a total follow-up time of 641,427 person-years. The study cohort with breastfeeding status available (all less than 52 weeks postpartum) included 94,817 women followed for 182,738 person-years. The study cohort with IUD type available was 322,898 women followed for 634,738 person-years. The crude incidence rate for uterine perforation is highest for the study population with information available on breastfeeding status, i.e., those who had an IUD insertion less than 52 weeks postpartum (pooled estimate, 3.68 per 1,000 person-years), compared with the other two study cohorts (pooled complete study population, incidence, 1.57 per 1,000 person-years, and pooled cohort with IUD type available, incidence, 1.57 per 1,000 person-years). This same pattern holds for the 1-year and 5-year cumulative incidence, which can be seen in Table 24 and Figure 11. This is consistent across all study sites (Table 24). Only about 1% of the complete study population did not have information on IUD type, and the crude incidence rates and cumulative incidence for the study population with information available on IUD type is nearly identical to the complete study population.

10.5.2 Uterine perforation and postpartum timing—first observed IUD insertions (objectives 4, 14, 15, 17)

10.5.2.1 Uterine perforation and postpartum timing incidence—first observed IUD insertions (objective 4: 14 weeks and 36 weeks postpartum categories)

Objective 4: To estimate the incidence rate and cumulative incidence of uterine perforation among women using IUDs for the following categories:

- *≤ 14 weeks postpartum*
- *> 14 weeks postpartum, including women without recorded delivery within the past 52 weeks*

- *≤ 36 weeks postpartum*
- *> 36 weeks postpartum, including women without recorded delivery within the past 52 weeks*

The crude incidence rate and 1- and 5-year cumulative incidence for uterine perforation for postpartum timing of IUD insertion ≤ 14 weeks, > 14 weeks, ≤ 36 weeks, and > 36 weeks are shown in Table 25.

Table 25: Crude incidence rate (per 1,000 person-years) and cumulative incidence of uterine perforation at 1 year and 5 years for first observed IUD insertions stratified by postpartum timing of IUD insertion; pooled and by research site

Research site and weeks postpartum	No. of insertions	Person-years	No. of events	Crude incidence rate (95% CI)	Crude cumulative incidence, 1 year (95 CI), %	Crude cumulative incidence, 5 years (95 CI), %
Pooled						
≤ 14	76,107	147,747.6	608	4.12 (3.79, 4.46)	0.58 (0.53, 0.65)	1.54 (1.38, 1.71)
> 14 or no delivery	250,551	493,679.7	400	0.81 (0.73, 0.89)	0.09 (0.08, 0.11)	0.33 (0.29, 0.38)
≤ 36	91,869	177,534.7	681	3.84 (3.55, 4.14)	0.55 (0.50, 0.60)	1.42 (1.29, 1.57)
> 36 or no delivery	234,789	463,892.5	327	0.70 (0.63, 0.79)	0.08 (0.06, 0.09)	0.30 (0.26, 0.34)
KPNC						
≤ 14	36,875	71,505.1	318	4.45 (3.97, 4.96)	0.59 (0.51, 0.68)	1.74 (1.50, 2.02)
> 14 or no delivery	124,567	254,046.4	211	0.83 (0.72, 0.95)	0.09 (0.07, 0.11)	0.38 (0.32, 0.45)
≤ 36	43,175	83,358.1	349	4.19 (3.76, 4.65)	0.56 (0.49, 0.64)	1.63 (1.41, 1.88)
> 36 or no delivery	118,267	242,193.4	180	0.74 (0.64, 0.86)	0.07 (0.06, 0.09)	0.35 (0.29, 0.42)
KPSC						
≤ 14	30,804	60,027.6	210	3.50 (3.04, 4.00)	0.55 (0.46, 0.64)	1.25 (1.04, 1.50)
> 14 or no delivery	92,410	181,895.6	114	0.63 (0.52, 0.75)	0.08 (0.06, 0.11)	0.22 (0.18, 0.28)
≤ 36	38,495	74,501.8	238	3.19 (2.80, 3.63)	0.50 (0.43, 0.58)	1.12 (0.94, 1.33)
> 36 or no delivery	84,719	167,421.4	86	0.51 (0.41, 0.63)	0.06 (0.05, 0.08)	0.19 (0.15, 0.25)
KPWA						
≤ 14	4,456	7,762.2	35	4.51 (3.14, 6.27)	0.63 (0.42, 0.94)	1.38 (0.93, 2.04)
> 14 or no delivery	16,070	29,734.0	29	0.98 (0.65, 1.40)	0.10 (0.06, 0.17)	0.30 (0.18, 0.50)
≤ 36	5,483	9,658.5	41	4.24 (3.05, 5.76)	0.59 (0.41, 0.86)	1.27 (0.89, 1.81)
> 36 or no delivery	15,043	27,837.7	23	0.83 (0.52, 1.24)	0.08 (0.05, 0.15)	0.26 (0.14, 0.47)

Research site and weeks postpartum	No. of insertions	Person-years	No. of events	Crude incidence rate (95% CI)	Crude cumulative incidence, 1 year (95 CI), %	Crude cumulative incidence, 5 years (95 CI), %
RI						
≤ 14	3,972	8,452.7	45	5.32 (3.88, 7.12)	0.76 (0.51, 1.12)	2.07 (1.46, 2.92)
> 14 or no delivery	17,504	28,003.6	46	1.64 (1.20, 2.19)	0.17 (0.11, 0.25)	0.66 (0.43, 1.01)
≤ 36	4,716	10,016.3	53	5.29 (3.96, 6.92)	0.74 (0.51, 1.07)	2.09 (1.52, 2.88)
> 36 or no delivery	16,760	26,440.0	38	1.44 (1.02, 1.97)	0.15 (0.10, 0.22)	0.55 (0.34, 0.89)

CI = confidence interval; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute.
Source: Analysis Tables 3.1 to 3.5.

For the pooled data and each research site, the incidence rates and cumulative incidence of uterine perforation are higher in the earlier postpartum IUD insertion group (≤ 14 weeks and ≤ 36 weeks) than in the group with later postpartum insertion (> 14 weeks and > 36 weeks) or insertion with no recorded delivery. Specifically, in the ≤ 14-week group, the crude incidence of uterine perforation pooled across sites is 4.12 per 1,000 person-years, and in the > 14-week group, the incidence is 0.81 per 1,000 person-years. In the ≤ 36-week group, the crude incidence pooled across research sites is 3.84 per 1,000 person-years and in the > 36-week group, 0.70 per 1,000 person-years. These results are consistent with the results of the 4-level postpartum categorization.

10.5.2.2 Uterine perforation and postpartum timing risk 14-week cut point—first observed IUD insertions (objective 14)

Objective 14: To estimate the adjusted hazard ratio of uterine perforation among women who had a first observed IUD insertion early in the postpartum period (i.e., up to 14 weeks postpartum) versus those who had a first observed IUD insertion late in the postpartum period (i.e., more than 14 weeks postpartum, including women without recorded delivery within the past 52 weeks)

The crude, propensity score–adjusted and fully adjusted HRs for uterine perforation at the first IUD insertion, for IUD insertion ≤ 14 weeks postpartum versus > 14 weeks postpartum or with no recorded delivery, are shown in Figure 12, pooled and by research site.

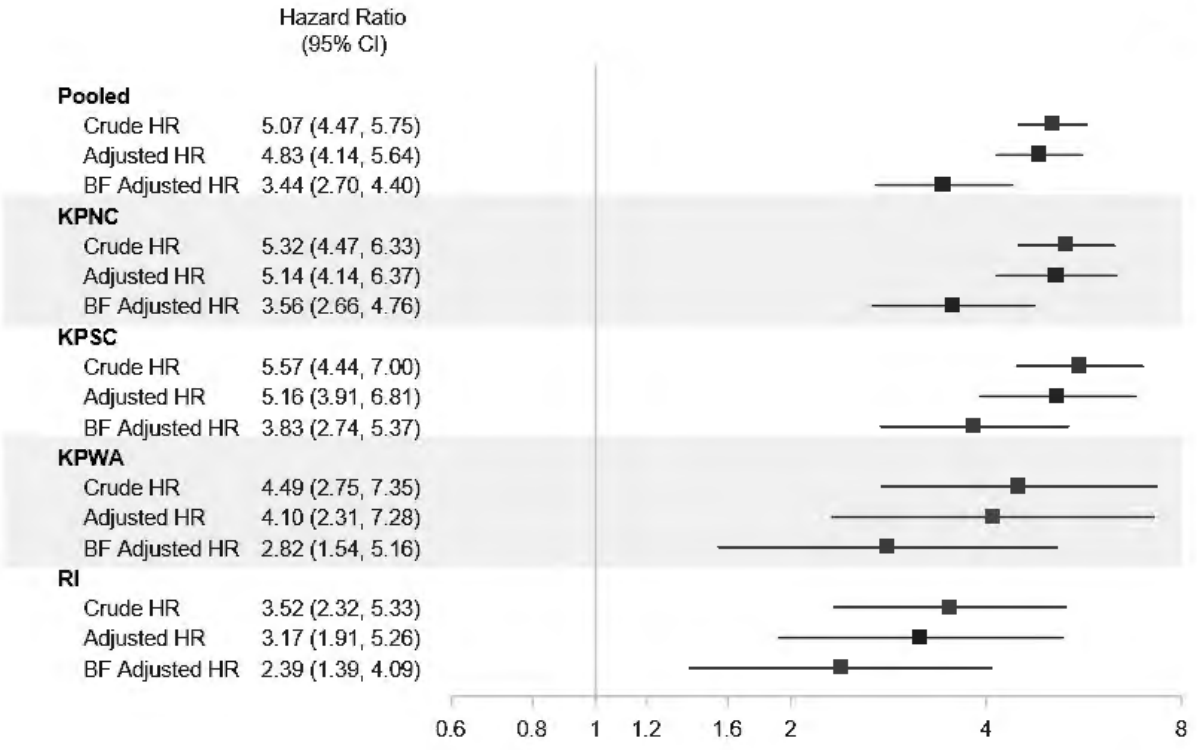


Figure 12: Crude, propensity score–adjusted, and fully adjusted hazard ratios for uterine perforation for ≤ 14 weeks postpartum at IUD insertion compared with those who were more than 14 weeks postpartum or with no recorded delivery; pooled across sites and by research site, first observed IUD insertions (source: data from Analysis Table 14.1)

Adjusted HR = adjusted for propensity scores; BF Adjusted HR or fully adjusted = adjusted for propensity scores and breastfeeding status; CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute

The complete study population was included in this analysis. The proportional hazards assumption was determined to be met based on visual inspection of the log-log survival curves. The same variables and propensity score scores used in the 4-level postpartum timing propensity score model were used for this analysis. The propensity scores were collapsed into the relevant exposure groups to evaluate the distribution of the propensity scores across the dichotomous exposure groups before and after weighting (before weighting, Analysis Tables 14.2.1-14.2.5; after weighting, Analysis Tables 14.3.1-14.3.5; before and after weighting, Analysis Figures 14.1.1-14.1.5). The only variable that was included in the propensity score model that remained unbalanced after weighting was BMI missing (KPWA), and it was only marginally unbalanced. Breastfeeding was not included in the propensity score model, but this variable was included as a covariate separate from the propensity score model.

As seen in the 4-level postpartum timing exposure analysis, uterine perforation was higher in the earlier postpartum group, here defined as ≤ 14 weeks, compared with women with an IUD inserted > 14 weeks postpartum or with no recorded delivery (crude HR, 5.07). Propensity score adjustment had minimal effect on the point estimates (HR, 4.83), and adjustment for propensity score and breastfeeding marginally attenuated the point estimates (HR, 3.44); however, the risk of uterine

perforation remained elevated for the group with IUD insertion ≤ 14 weeks postpartum at all sites and in all models.

10.5.2.3 Uterine perforation and postpartum timing risk 36-week cut point—first observed IUD insertions (objective 15)

Objective 15: To estimate the adjusted hazard ratio of uterine perforation among women who had a first observed IUD insertion ≤ 36 weeks postpartum versus women who had a first observed IUD insertion > 36 weeks postpartum, including women without recorded delivery within the past 52 weeks (this objective will be performed as a sensitivity analysis; same cut point as in EURAS-IUD)

The crude, propensity score–adjusted and fully adjusted HRs for uterine perforation with IUD insertion ≤ 36 weeks postpartum versus > 36 weeks postpartum or no recorded delivery, for first IUD insertion, are in Figure 13, pooled and by research site.

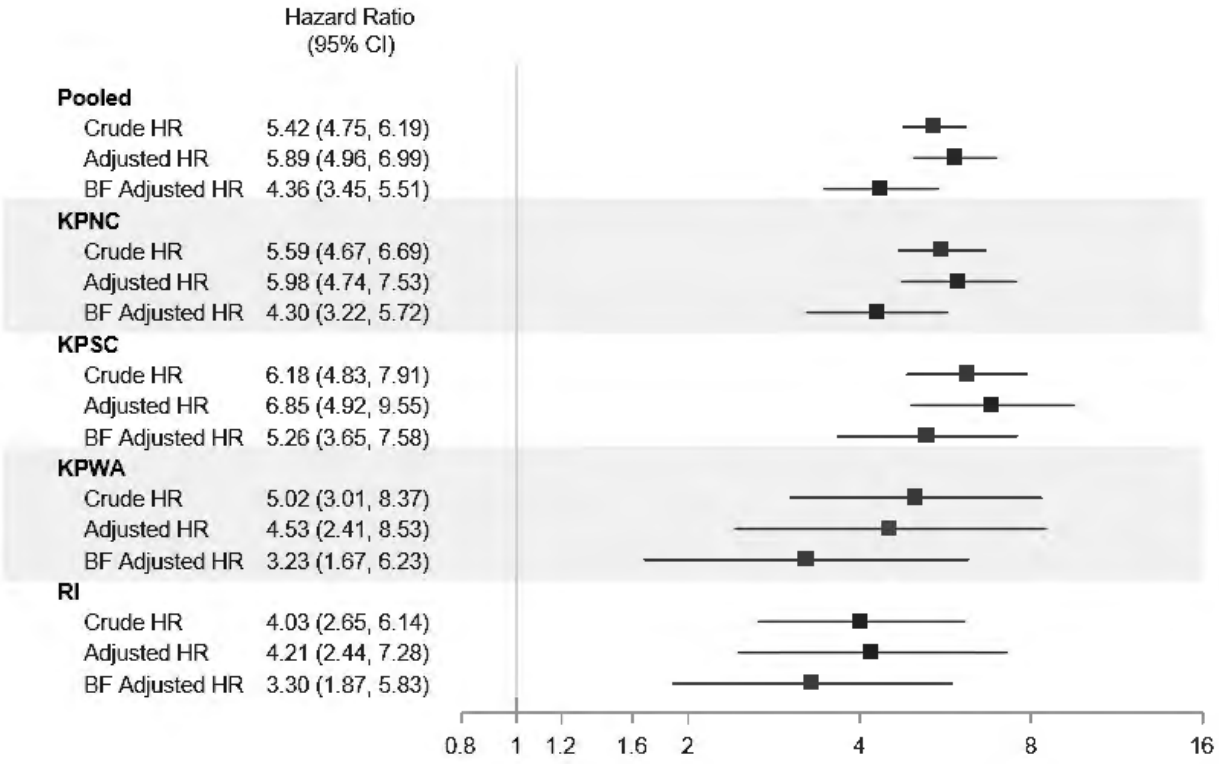


Figure 13: Crude, propensity score–adjusted, and fully adjusted hazard ratios for uterine perforation for ≤ 36 weeks postpartum at IUD insertion compared with those who were more than 36 weeks postpartum or with no recorded delivery; pooled across sites and by research site, first observed IUD insertions (source: data from Analysis Table 15.1)

Adjusted HR = adjusted for propensity scores; BF Adjusted HR or fully adjusted = adjusted for propensity scores and breastfeeding status; CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute

The complete study population was included in this analysis. The proportional hazards assumption was determined to be met based on visual inspection of the curves. The same variables and

propensity scores used in the 4-level postpartum timing propensity score model were used for this analysis. The propensity scores were collapsed into the relevant exposure groups to evaluate the distribution of the propensity scores across the dichotomous exposure groups before and after weighting (before weighting, Analysis Tables 15.2.1-15.2.5; after weighting, Analysis Tables 15.3.1-15.3.5; before and after weighting, Analysis Figures 15.1.1-15.1.5). The only variables that were included in the propensity score model that remained unbalanced after weighting were race/ethnicity Hispanic other (KPSC) and BMI missing (KPWA), and they were only marginally unbalanced. Breastfeeding was not included in the propensity score model, but this variable was included as a covariate separate from the propensity score model.

As seen in the 4-level postpartum timing exposure analysis and the 14-week dichotomous timing categories, uterine perforation was higher in the group with IUD insertion earlier postpartum, here defined as ≤ 36 weeks, compared with those with an IUD inserted > 36 weeks postpartum or with no recorded delivery (pooled crude HR, 5.42). Propensity score adjustment had minimal effect on the point estimates (pooled adjusted HR, 5.89); adjustment for propensity score and breastfeeding status attenuated the point estimate (HR, 4.36), but the risk of uterine perforation remained elevated for the group with IUD insertion ≤ 36 weeks postpartum at all sites and in all models.

10.5.2.4 Uterine perforation and postpartum timing incidence rate ratios and differences 36-week cut point—first observed IUD insertions (objective 17)

Objective 17: To estimate the adjusted incidence rate ratio (IRR) and incidence rate difference (IRD) of uterine perforation at 1 year and 5 years of follow-up among women who had a first observed IUD insertion ≤ 36 weeks postpartum versus women who had a first observed IUD insertion > 36 weeks postpartum, including women without recorded delivery within the past 52 weeks (same analytic approach as EURAS-IUD)

The crude incidence rates and crude and propensity score–adjusted IRRs for uterine perforation, stratified by breastfeeding status, with IUD insertion ≤ 36 weeks postpartum versus > 36 weeks postpartum or no recorded delivery for first IUD insertion, pooled across research sites, are shown in Table 26 and Figure 14. The IRDs, pooled across all sites, are shown in Table 27. The complete study population was included in this analysis. Adjustment was done via weighted estimation of the rates using overlap weights derived from the same propensity score models as those developed for adjustment of the HRs for the 36-week cut point.

Table 26: Number of events, person-time of follow-up, and crude incidence rates (per 1,000 person-years) for uterine perforation, ≤ 36 weeks postpartum at IUD insertion and > 36 weeks postpartum or with no recorded delivery, at 1 year of follow-up and 5 years of follow-up, overall and stratified by breastfeeding status; complete study population, pooled across research sites, first observed IUD insertions

Breastfeeding status	Measure	1 year of follow-up		5 years of follow-up	
		≤ 36 weeks	> 36 weeks or no delivery	≤ 36 weeks	> 36 weeks or no delivery
Overall	# Events	430	152	662	300
	Person-years	71,595.2	182,233.7	172,863.3	453,355.2
	Crude incidence rate	6.01	0.83	3.83	0.66
Yes	# Events	326	7	503	8
	Person-years	49,483.8	1,178.7	118,178.2	2,708.0
	Crude incidence rate	6.59	5.94	4.26	2.95
No	# Events	88	142	138	288
	Person-years	20,209.5	180,715.9	50,080.3	449,784.8
	Crude incidence rate	4.35	0.79	2.76	0.64
Undetermined	# Events	16	3	21	4
	Person-years	1,901.9	339.1	4,604.8	862.4
	Crude incidence rate	8.41	8.85	4.56	4.64

IUD = intrauterine device.
Source: Analysis Tables 17.1-17.5 (pooled and by research site).

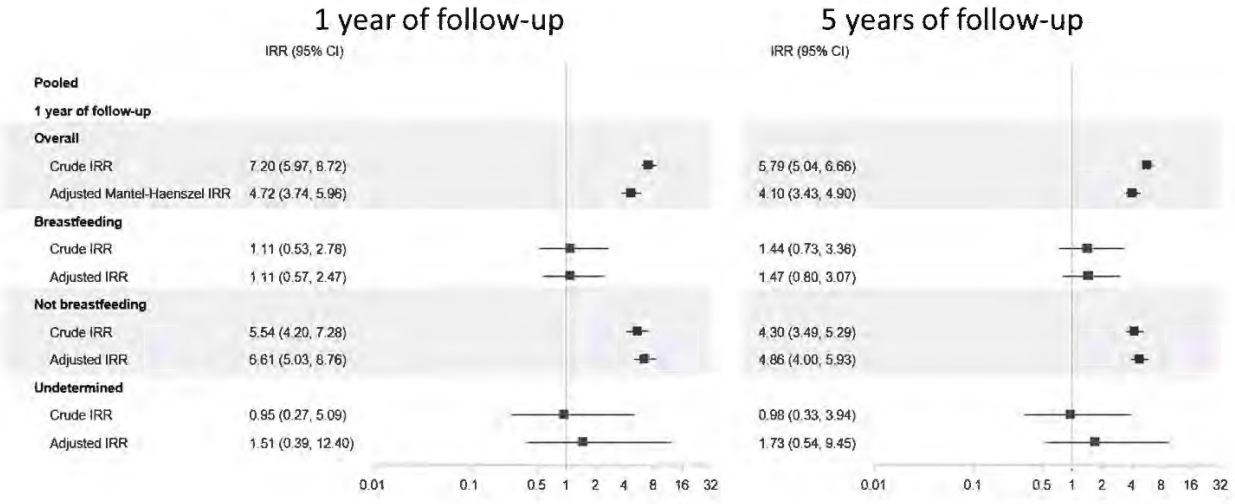


Figure 14: Crude and adjusted incidence rate ratios (overall and stratified by breastfeeding status at the time of IUD insertion) for uterine perforation for ≤ 36 weeks postpartum at IUD insertion versus > 36 weeks postpartum or with no recorded delivery, 1 year of follow-up and 5 years of follow-up; complete study population, pooled across research sites, first observed IUD insertions (source: data from Analysis Tables 17.1-17.5, pooled and by research site)

CI = confidence interval; IRR = incidence rate ratio.

The crude incidence rates are in Table 26. The crude incidence rates of uterine perforation in women who were ≤ 36 weeks postpartum at IUD insertion, regardless of breastfeeding status, are approximately 4 to 8 times higher than women who were not breastfeeding and were > 36 weeks postpartum or with no recorded delivery at IUD insertion. At both 1 and 5 years of follow-up, the highest incidence rate of uterine perforation, among those with known breastfeeding status, is in the group that had their IUD inserted ≤ 36 weeks postpartum and while breastfeeding. The lowest incidence is in the group with IUDs inserted > 36 weeks postpartum (or with no recorded delivery) who were not breastfeeding. As seen in the previous analyses of postpartum timing and uterine perforation with a 36-week cut point (incidence rates [Table 25] and HRs [Figure 12]), in the IRR, estimates pooled across sites at 1 and 5 years of follow-up (Figure 14), the risk of uterine perforation was higher in the earlier postpartum group (≤ 36 weeks) than in women with an IUD inserted > 36 weeks postpartum or with no recorded delivery (Figure 14). However, the elevated risk of earlier postpartum IUD insertion is most obvious among those who were not breastfeeding at the time of IUD insertion. Among those who were breastfeeding, earlier postpartum IUD insertion was associated with minimal, if any, additional risk of uterine perforation. A formal test of interaction between postpartum timing and breastfeeding status among women who were all within 52 weeks of delivery at the time of IUD insertion is described in Section 10.5.10.1.

Table 27: Crude and adjusted[a] incidence rate differences (per 1,000 person-years) for uterine perforation for women ≤ 36 weeks postpartum at IUD insertion compared with those who were > 36 weeks postpartum or with no recorded delivery, 1 year of follow-up and 5 years of follow-up, overall and stratified by breastfeeding status; complete study population, pooled across research sites, first observed IUD insertions

Breastfeeding status	Statistic	1 year of follow-up		5 years of follow-up	
		≤ 36 weeks IRD (95% CI)	> 36 weeks or no delivery	≤ 36 weeks IRD (95% CI)	> 36 weeks or no delivery
Overall	Crude IRD	5.17 (4.59, 5.75)	Reference	3.17 (2.87, 3.47)	Reference
	Adjusted IRD[b]	3.75 (3.05, 4.45)	Reference	2.28 (1.93, 2.63)	Reference
Yes	Crude IRD	0.65 (−3.81, 5.11)	Reference	1.30 (−0.78, 3.38)	Reference
	Adjusted IRD	0.63 (−3.39, 4.64)	Reference	1.38 (−0.46, 3.21)	Reference
No	Crude IRD	3.57 (2.65, 4.49)	Reference	2.12 (1.65, 2.58)	Reference
	Adjusted IRD	3.92 (3.22, 4.63)	Reference	2.33 (1.97, 2.69)	Reference
Undetermined	Crude IRD	−0.43 (−11.26, 10.39)	Reference	−0.08 (−5.02, 4.87)	Reference
	Adjusted IRD	2.74 (−5.09, 10.57)	Reference	1.99 (−1.49, 5.47)	Reference

CI = confidence interval; IRD = incidence rate difference; IUD = intrauterine device.
[a] Adjusted via weighted estimation of the rates using overlap weights derived from the same propensity score models as those developed for adjustment of the hazard ratios.
[b] Mantel-Haenszel estimate.
Source: Analysis Tables 17.1-17.5, pooled and by research site.

The IRDs show a pattern similar to that of the IRRs with overall an additional 3.75 uterine perforations per 1,000 person-years in the early postpartum insertion group compared with the later postpartum insertion group at 1 year and 2.28 additional perforations per 1,000 person-years at 5 years of follow-up. The estimates for those with earlier postpartum timing who were not breastfeeding were 3.9 additional perforations per 1,000 person-years at 1 year and 2.3 additional perforations per 1,000 person-years at 5 years. Among those who were breastfeeding, earlier postpartum timing compared to those with IUD insertions > 36 weeks, was not associated with a

significantly higher number of perforations at 1 year or 5 years after insertion, even though the absolute incidence rate is highest in this group.

10.5.3 Uterine perforation and IUD type—first observed IUD insertions (objectives 6, 16)

10.5.3.1 Uterine perforation and IUD type incidence—first observed IUD insertions (objective 6)

Objective 6: To estimate the incidence rate and cumulative incidence of uterine perforation among women with different types of IUD (i.e., LNG-IUD and copper IUD)

The crude incidence rate and 1- and 5-year cumulative incidence for uterine perforation by IUD type (LNG, Copper, unknown) are shown in Table 28 and Figure 15. The data are not presented by research site in agreement with the Kaiser Permanente Data Use Agreement.

Table 28: Crude incidence rate (per 1,000 person-years) and cumulative incidence of uterine perforation at 1 year and 5 years, first observed IUD insertions, stratified by IUD type; pooled across research sites

IUD type	No. of insertions	Person-years	No. of events	Crude incidence rate (95% CI)	Crude cumulative incidence, 1 year (95% CI), %	Crude cumulative incidence, 5 years (95% CI), %
LNG-IUD	259,234	507,151.2	834	1.64 (1.53, 1.76)	0.22 (0.20, 0.24)	0.63 (0.57, 0.68)
Copper IUD	63,664	127,587.0	162	1.27 (1.08, 1.48)	0.16 (0.13, 0.20)	0.55 (0.44, 0.68)
Unknown	3,760	6,689.1	12	1.79 (0.93, 3.13)	0.33 (0.18, 0.60)	0.41 (0.22, 0.75)

CI = confidence interval; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.
Source: Analysis Tables 3.1 to 3.5.

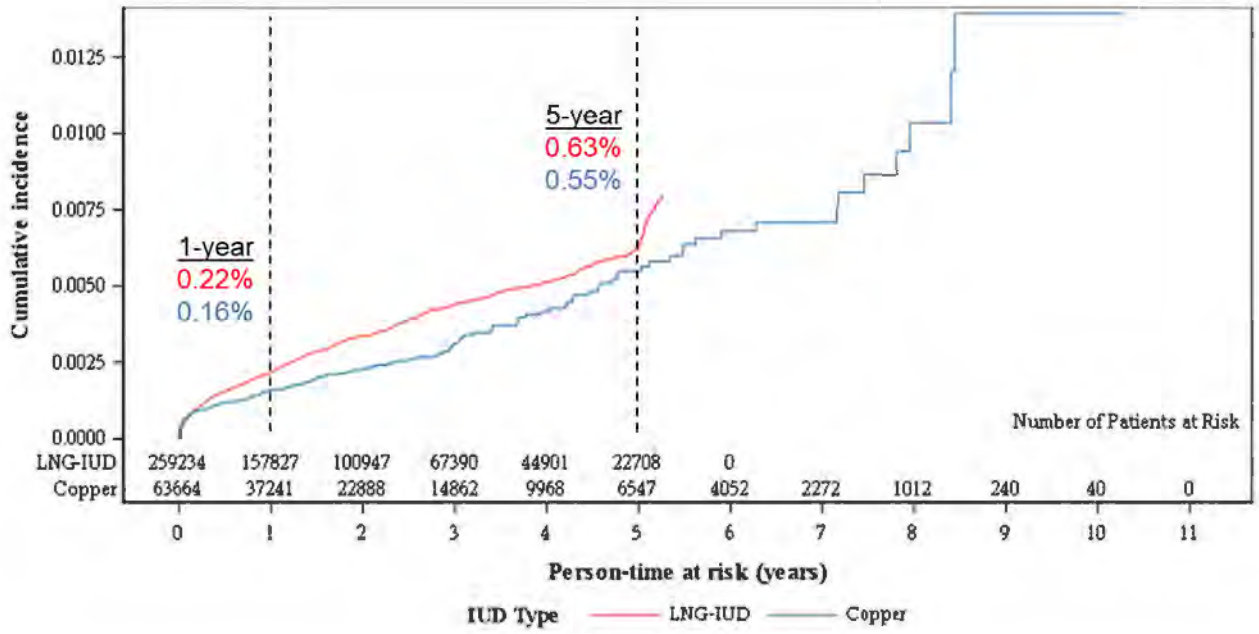


Figure 15: Crude cumulative incidence of uterine perforation pooled across sites by IUD type (source: data from Analysis Table 3.1, Analysis Figure 6.1)

IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.

The crude incidence rate and cumulative incidence of uterine perforation at 1 and 5 years are somewhat higher among those with LNG-IUDs versus copper IUDs (crude incidence per 1,000 person-years: LNG-IUDs, 1.64; copper, 1.27). Labeled IUD expiration was used as a censoring event for these analyses. As can be seen in Figure 15, the number of uterine perforations diagnosed increased right around 5 years after IUD insertion, which likely reflects the uterine perforations that were recognized at the time the woman returned to have the IUD removed because most of the LNG-IUDs were Mirena with a 5-year expiration. This trend is less obvious around the 10-year expiration for copper IUDs because only the two smaller research sites had the potential for 10 years of follow-up, and the sample size dropped rapidly after 6 years of follow-up.

10.5.3.2 Risk of uterine perforation by IUD type—first observed IUD insertions (objective 16)

Objective 16: To estimate the adjusted hazard ratio of uterine perforation for women whose first observed IUD was an LNG-releasing IUD versus women whose first observed IUD was a copper IUD

The crude and propensity score–adjusted HRs for the comparison of LNG-IUDs with copper IUDs and uterine perforation for first IUD insertions are shown in Figure 16, pooled across research sites.

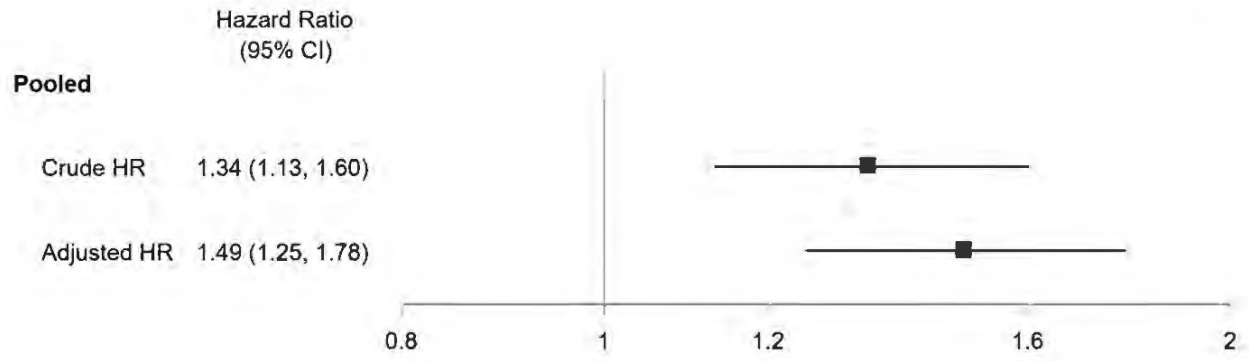


Figure 16: Hazard ratios (crude and propensity score–adjusted) for uterine perforation for LNG-IUDs compared with copper IUDs; pooled across sites, first observed IUD insertions (source: data from Analysis Table 16.1)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.

The study population with IUD type available (those with unknown IUD type were removed) was included for this analysis. The proportional hazards assumption was satisfied. Standardized differences prior to confounding adjustment were modest, i.e., only one variable had a value for the absolute standardized difference > 0.2 (Analysis Table 16.2.1 and Analysis Figure 16.1.1). After propensity score weighting, all of the variables included in the model had satisfactory balance (absolute standardized difference < 0.2) (Analysis Table 16.3.1 and Analysis Figure 16.1.1).

The risk of uterine perforation was significantly higher for LNG-IUDs than for copper IUDs; propensity score adjustment did not attenuate the point estimate (crude HR, 1.34; adjusted HR, 1.49).

10.5.4 Uterine perforation and menorrhagia—first observed IUD insertions (objectives 7, 19, and additional analyses)

10.5.4.1 Uterine perforation and menorrhagia incidence—first observed IUD insertions (objective 7: complete study population [per protocol] and excluding those with a delivery in the previous 52 weeks [additional analysis])

Objective 7: To estimate the incidence rate and cumulative incidence of uterine perforation among women with and without menorrhagia (heavy menstrual bleeding) in the 12 months before IUD insertion

The crude incidence rate for and 1- and 5-year cumulative incidence of uterine perforation by menorrhagia status for the complete study population and the study population of women more than 52 weeks postpartum or with no recorded delivery, including nulliparous women (additional analysis) are shown in Table 29. Figure 17 displays the cumulative incidence of uterine perforation over follow-up time stratified by whether the woman had a diagnosis of menorrhagia in the year prior to IUD insertion, for the complete study population. Figure 18 includes the data for the study population without a delivery in the previous 52 weeks (additional analysis).

Table 29: Crude incidence rate (per 1,000 person-years) and cumulative incidence of uterine perforation at 1 year and 5 years, first observed IUD insertions stratified by menorrhagia status; pooled and by research site, complete study population and study population of women more than 52 weeks postpartum or with no recorded delivery

Research site and menorrhagia in the past year	No. of insertions	Person-years	No. of events	Crude incidence rate (95% CI)	Crude cumulative incidence, 1 year (95 CI), %	Crude cumulative incidence, 5 years (95 CI), %
Complete study population						
Pooled						
Yes	32,552	64,034.5	64	1.00 (0.77, 1.28)	0.10 (0.07, 0.14)	0.41 (0.31, 0.56)
No	294,106	577,392.7	944	1.63 (1.53, 1.74)	0.22 (0.20, 0.24)	0.63 (0.58, 0.69)
KPNC						
Yes	13,593	27,023.3	27	1.00 (0.66, 1.45)	0.09 (0.05, 0.17)	0.43 (0.27, 0.68)
No	147,849	298,528.2	502	1.68 (1.54, 1.84)	0.21 (0.19, 0.24)	0.70 (0.62, 0.78)
KPSC						
Yes	15,727	30,649.3	27	0.88 (0.58, 1.28)	0.09 (0.05, 0.16)	0.37 (0.23, 0.59)
No	107,487	211,273.9	297	1.41 (1.25, 1.58)	0.22 (0.19, 0.25)	0.49 (0.42, 0.57)
KPWA						
Yes	2,027	3,898.6	3	0.77 (0.16, 2.25)	0.12 (0.03, 0.50)	0.24 (0.07, 0.77)
No	18,499	33,597.6	61	1.82 (1.39, 2.33)	0.23 (0.17, 0.32)	0.56 (0.40, 0.77)
RI						
Yes	1,205	2,463.3	7	2.84 (1.14, 5.85)	0.28 (0.09, 0.86)	1.11 (0.49, 2.53)
No	20,271	33,993.0	84	2.47 (1.97, 3.06)	0.28 (0.21, 0.38)	0.99 (0.73, 1.34)
Study population more than 52 weeks postpartum or with no recorded delivery						
Pooled						
Yes	31,600	62,405.4	61	0.98 (0.75, 1.26)	0.09 (0.06, 0.14)	0.39 (0.29, 0.53)
No	197,234	390,598.3	248	0.63 (0.56, 0.72)	0.07 (0.06, 0.08)	0.28 (0.24, 0.33)
KPNC						
Yes	13,204	26,366.7	26	0.99 (0.64, 1.44)	0.09 (0.05, 0.17)	0.39 (0.25, 0.63)
No	102,307	210,809.5	147	0.70 (0.59, 0.82)	0.07 (0.05, 0.09)	0.34 (0.28, 0.41)
KPSC						
Yes	15,297	29,916.5	25	0.84 (0.54, 1.23)	0.08 (0.04, 0.14)	0.34 (0.21, 0.56)
No	66,848	132,799.2	54	0.41 (0.31, 0.53)	0.05 (0.04, 0.07)	0.15 (0.11, 0.22)

Research site and menorrhagia in the past year	No. of insertions	Person-years	No. of events	Crude incidence rate (95% CI)	Crude cumulative incidence, 1 year (95 CI), %	Crude cumulative incidence, 5 years (95 CI), %
KPWA						
Yes	1,961	3,779.1	3	0.79 (0.16, 2.32)	0.13 (0.03, 0.52)	0.24 (0.07, 0.80)
No	12,740	23,470.8	18	0.77 (0.45, 1.21)	0.06 (0.03, 0.13)	0.25 (0.13, 0.52)
RI						
Yes	1,138	2,343.0	7	2.99 (1.20, 6.16)	0.29 (0.09, 0.91)	1.17 (0.51, 2.67)
No	15,339	23,518.9	29	1.23 (0.83, 1.77)	0.12 (0.08, 0.20)	0.49 (0.27, 0.89)

CI = confidence interval; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute.
Source: Analysis Tables 3.1 to 3.5 and Additional Analysis Table 3.13.

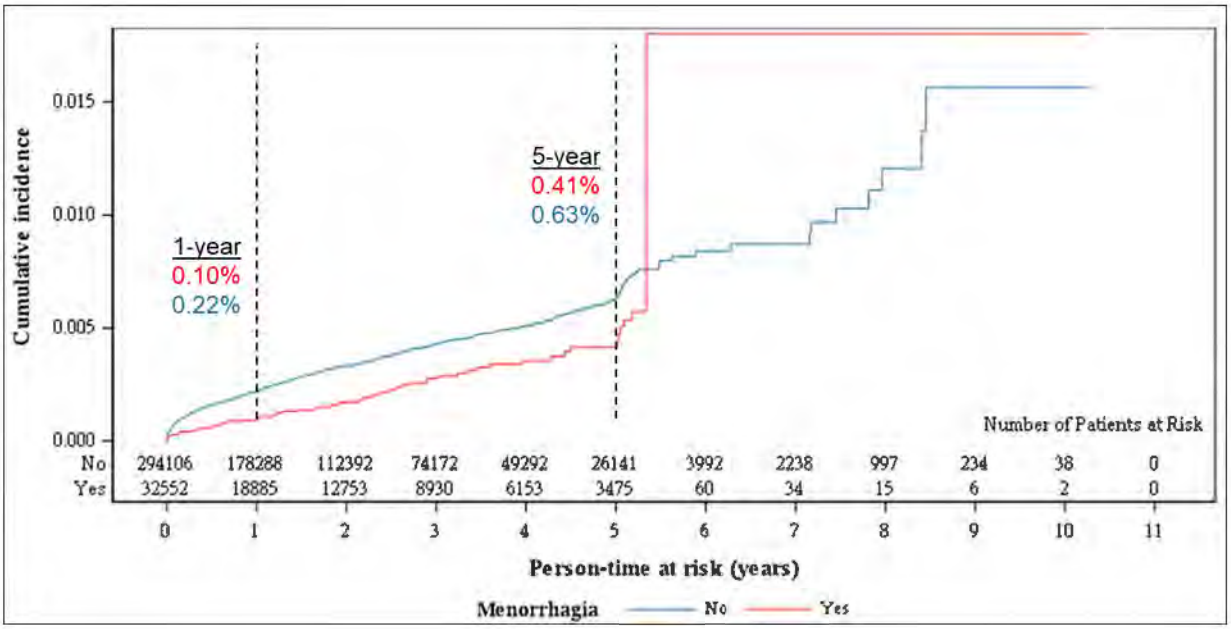


Figure 17: Crude cumulative incidence of uterine perforation by menorrhagia status for the pooled complete study population (source: data from Analysis Table 3.1, Analysis Figure 7.1)

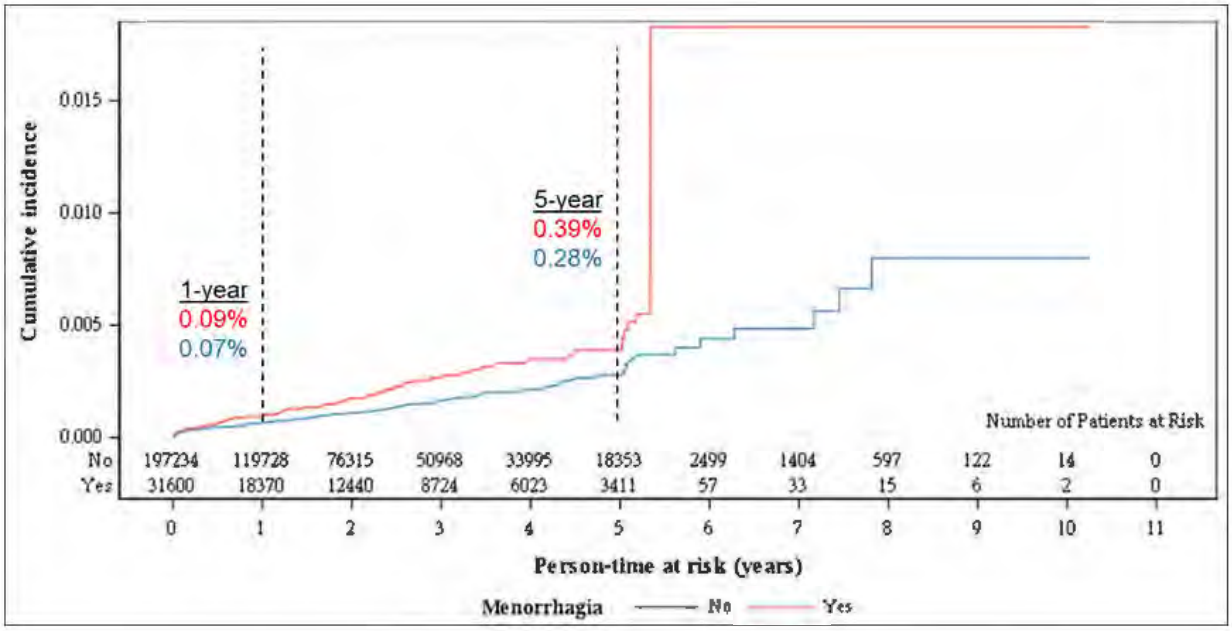


Figure 18: Crude cumulative incidence of uterine perforation by menorrhagia status for the pooled study population excluding women with a delivery in the previous 52 weeks (source: data from Additional Analysis Table 3.13, Additional Analysis Figure 7.2.1)

For the complete study population, the crude incidence rates and cumulative incidence at 1 and 5 years for uterine perforation are lower among those with menorrhagia for the pooled data and for each site except RI, where the estimates are very similar (Table 29). Wide CIs were noted among those with menorrhagia at KPWA and RI due to a small number of events. When restricting these analyses to the study population of women without a recorded delivery in the previous 52 weeks, the population of most clinical interest for the impact of menorrhagia, then the crude incidence rates and cumulative incidence at 1 and 5 years for uterine perforation are somewhat higher among those with menorrhagia for the pooled data and for each site except the KPWA 5-year cumulative incidence.

10.5.4.2 Uterine perforation and menorrhagia risk—first observed IUD insertions (objective 19)

Objective 19: To estimate the adjusted hazard ratio of uterine perforation for women using an IUD who have at least one diagnosis code indicating menorrhagia in the 12 months before IUD insertion versus IUD users who do not have this indication; separate analyses for the complete study population and women without a delivery in the previous 52 weeks

The crude and propensity score–adjusted HRs for menorrhagia and uterine perforation for the complete study population first IUD insertion, pooled across research sites, are displayed in Figure 19. We also conducted an additional analysis in the study population that included only women without a delivery in the previous 52 weeks since a diagnosis of menorrhagia would be much less likely in a recent postpartum group. Those results are in Figure 20.

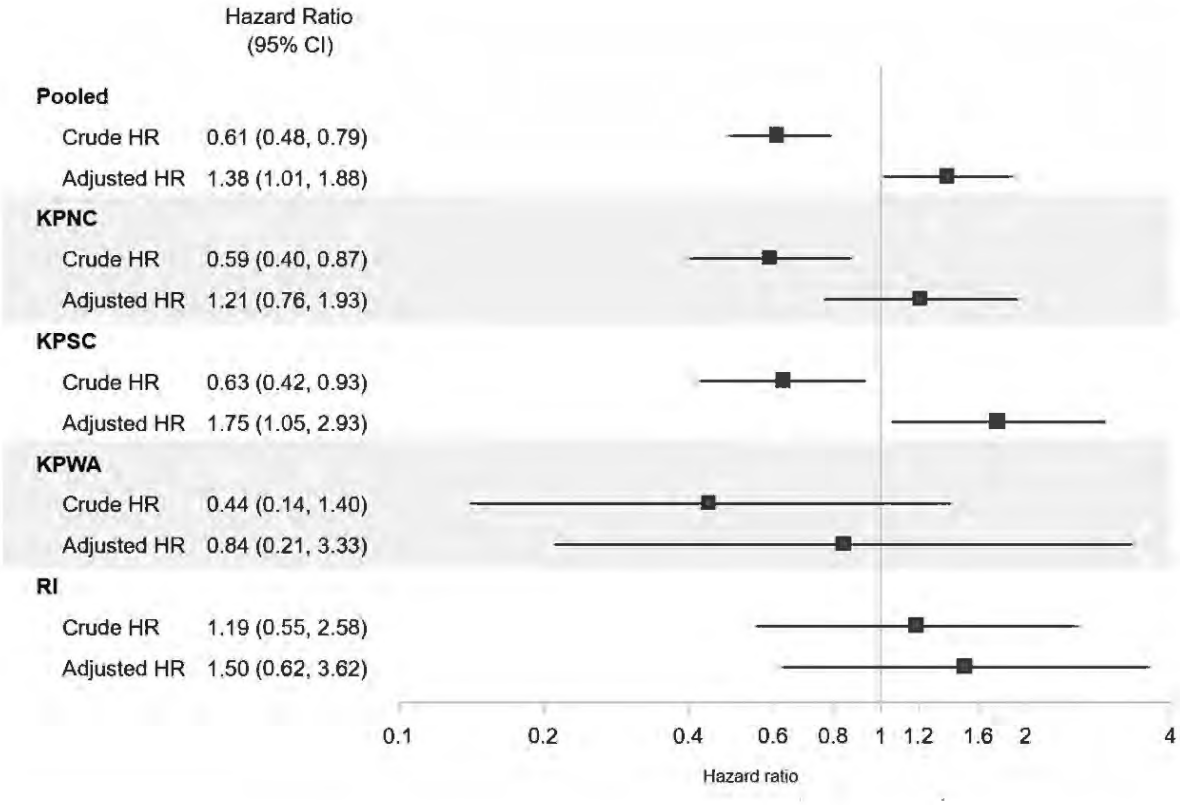


Figure 19: Crude and propensity score–adjusted hazard ratios for uterine perforation in women with a history of menorrhagia at IUD insertion compared with women who did not have a history of menorrhagia; pooled and by site, complete study population, first observed IUD insertions (source: data from Analysis Table 19.1, pooled and by research site)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute.

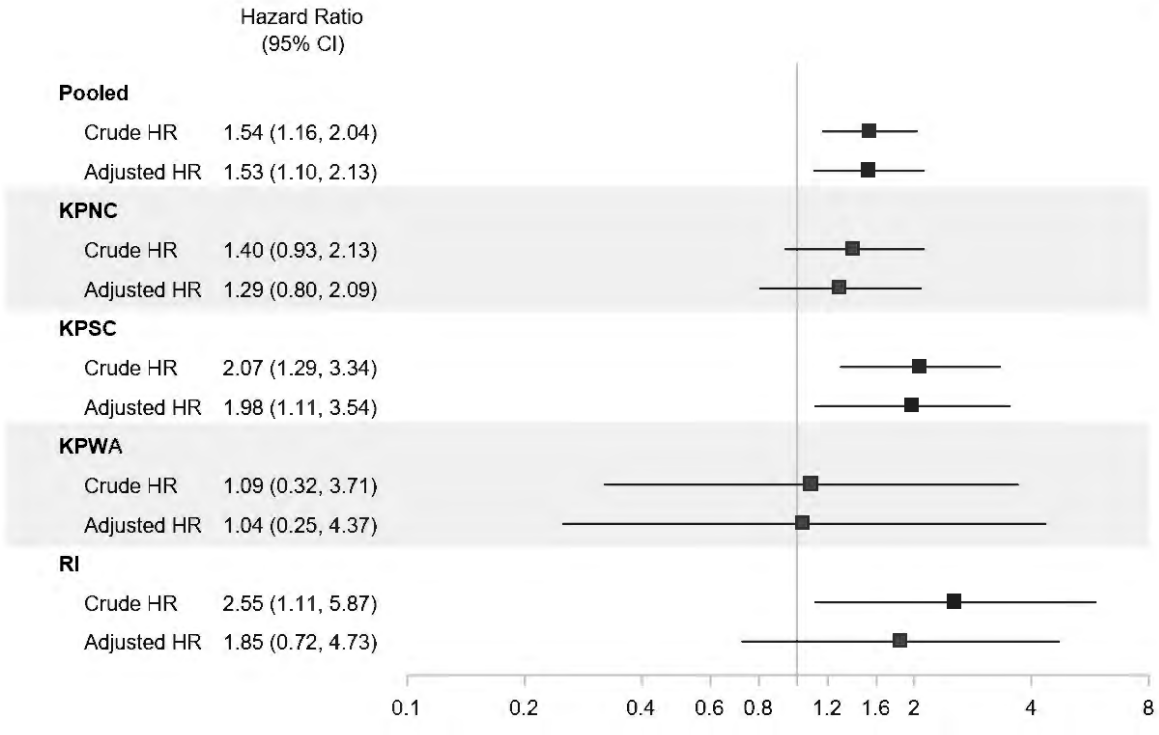


Figure 20: Crude and propensity score–adjusted hazard ratios for uterine perforation in women with a history of menorrhagia at IUD insertion compared with women who did not have a history of menorrhagia; pooled and by site, including only women without a delivery in the previous 52 weeks, first observed IUD insertions (source: data from Analysis Table 19.4)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute.

In crude analyses, women with menorrhagia in the past year were *less* likely to have uterine perforation than women who did not have menorrhagia in the past year. The proportional hazards assumption was satisfied through 5 years after insertion. Standardized differences prior to confounding adjustment were substantial (pooled: Analysis Table 19.2.1; by site: Analysis Tables 19.2.2-19.2.5). After propensity score weighting using initial propensity score models, all levels of all variables had satisfactory balance (absolute standardized difference < 0.2), overall and at all sites except RI, where dysmenorrhea, concomitant gynecological procedure, and any difficult insertion were less well balanced (absolute standardized difference, 0.2-0.3) (Analysis Tables 19.3.1-19.3.5 and Analysis Figures 19.1.1-19.1.5).

In the complete study population, after adjustment, women with menorrhagia in the past year were *more* likely to have uterine perforation than women who did not have menorrhagia in the past year (pooled adjusted HR, 1.38). The patterns for each research site were generally consistent with the pooled results, with an increase in the HR after adjustment. In the population of women without a delivery in the previous 52 weeks, those with a diagnosis of menorrhagia were more likely to have a uterine perforation than those without a menorrhagia diagnosis in the previous 12 months in both the crude and adjusted HRs (pooled crude HR, 1.54; adjusted HR, 1.53) (Figure 20). The crude and adjusted HRs were much more comparable in the population without a delivery in the previous 52 weeks (Figure 20) than they were for the complete study population (Figure 19), suggesting that

including women who had a recent delivery confounded the association between menorrhagia and uterine perforation. In both study populations, the adjusted HRs are consistent with a 40%-50% higher risk of uterine perforation in women with a diagnosis of menorrhagia in the previous year.

10.5.5 IUD expulsion, for women using IUDs—first observed IUD insertions (objective 8)

Objective 8: To estimate the incidence rate and cumulative incidence of IUD expulsion among users of IUDs

The crude incidence rate for and 1- and 5-year cumulative incidence of IUD expulsion for the three study populations—complete, breastfeeding status available, IUD type available—are shown in Table 30 and Figure 21.

Table 30: Crude incidence rate (per 1,000 person-years) and cumulative incidence of IUD expulsion at 1 year and 5 years, first observed IUD insertions for the complete, breastfeeding, and IUD type study populations; pooled and by research site

Research site and study population	No. of inser-tions	Person-years	No. of events	Crude incidence rate (95% CI)	Crude cumulative incidence, 1 year (95 CI), %	Crude cumulative incidence, 5 years (95 CI), %
Pooled						
Complete study population	326,658	641,427.2	8,943	13.94 (13.65, 14.23)	2.29 (2.24, 2.35)	4.57 (4.45, 4.68)
Breastfeeding status available	94,817	182,738.4	2,126	11.63 (11.14, 12.14)	1.83 (1.74, 1.93)	3.83 (3.64, 4.04)
IUD type available	322,898	634,738.1	8,872	13.98 (13.69, 14.27)	2.30 (2.24, 2.36)	4.57 (4.46, 4.69)
KPNC[a]						
Complete study population	161,442	325,551.5	5,035	15.47 (15.04, 15.90)	2.48 (2.40, 2.56)	5.29 (5.12, 5.47)
Breastfeeding status available	45,353	87,388.5	1,215	13.90 (13.13, 14.71)	2.15 (2.01, 2.30)	4.70 (4.38, 5.04)
KPSC[a]						
Complete study population	123,214	241,923.2	3,172	13.11 (12.66, 13.58)	2.31 (2.22, 2.40)	3.97 (3.81, 4.14)
Breastfeeding status available	40,706	78,471.1	751	9.57 (8.90, 10.28)	1.55 (1.43, 1.69)	2.95 (2.71, 3.20)
KPWA[a]						
Complete study population	20,526	37,496.2	436	11.63 (10.56, 12.77)	1.74 (1.55, 1.96)	4.12 (3.67, 4.63)
Breastfeeding status available	4,839	8,841.7	92	10.41 (8.39, 12.76)	1.59 (1.24, 2.04)	3.67 (2.80, 4.79)
RI[a]						
Complete study population	21,476	36,456.3	300	8.23 (7.32, 9.21)	1.26 (1.11, 1.44)	2.44 (2.08, 2.86)
Breastfeeding status available	3,919	8,037.1	68	8.46 (6.57, 10.73)	1.32 (0.98, 1.77)	3.01 (2.23, 4.05)

CI = confidence interval; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute. [a] Site-specific results for the IUD type population are not presented at the request of Kaiser research sites. Source: Analysis Tables 8.1 to 8.5.

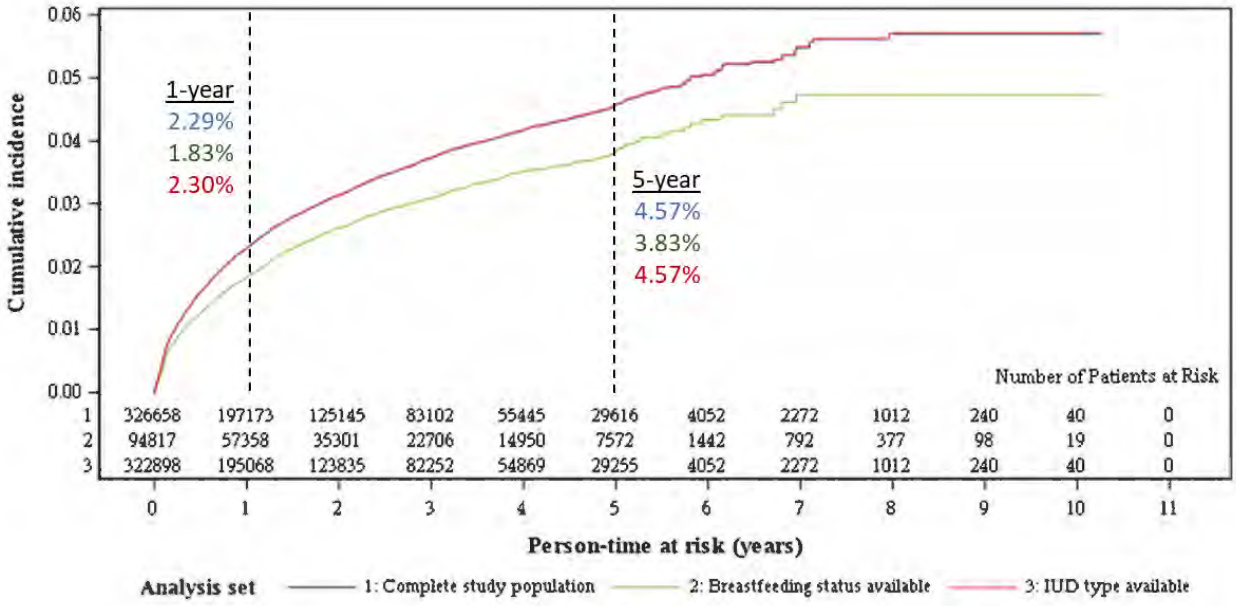


Figure 21: Crude cumulative incidence of IUD expulsion; pooled across sites for the three study populations: complete, breastfeeding status available, and IUD type (source: data from Analysis Tables 8.1 to 8.5)

IUD = intrauterine device.

The complete study population included 326,658 women with an IUD insertion with a total follow-up time of 641,427 person-years. The study cohort with breastfeeding status available (all less than 52 weeks postpartum) included 94,817 women followed for 182,738 person-years. The study cohort with IUD type available was 322,898 women followed for 634,738 person-years. The crude incidence rate for IUD expulsion was lower for the study population with information available on breastfeeding status (i.e., those who had an IUD insertion less than 52 weeks postpartum) than the other two study populations (pooled crude incidence rates per 1,000 person-years: complete study population, 13.94; breastfeeding cohort, 11.63; IUD type cohort, 13.98). This same pattern held for the 1-year and 5-year cumulative incidence, which can be seen in Table 30 and Figure 21. The information on the complete study population and breastfeeding population was consistent across all study sites except RI, where incidence was approximately the same for the breastfeeding and complete study populations (Table 30). Only about 1% of the complete study population did not have information on IUD type, and the crude incidence rates and cumulative incidence for IUD expulsion for the study population with information available on IUD type were nearly identical to those for the complete study population (Figure 21).

10.5.6 IUD expulsion and postpartum timing—first observed IUD insertions (objectives 9, 21, 22, 23, 25)

10.5.6.1 IUD expulsion and postpartum timing incidence—first observed IUD insertions (objective 9 and additional categories)

Objective 9: To estimate the incidence rate and cumulative incidence of IUD expulsion among women using IUDs for the following categories:

- *≤ 3 days postpartum (not in objective 9, category added)*
- *> 3 days and ≤ 6 weeks postpartum (not in objective 9, category added)*
- *≤ 6 weeks postpartum*
- *> 6 weeks and ≤ 14 weeks postpartum*
- *> 14 weeks and ≤ 52 weeks postpartum*
- *> 52 weeks postpartum, including women without recorded delivery within the past 52 weeks*
- *≤ 14 weeks postpartum*
- *> 14 weeks postpartum, including women without recorded delivery within the past 52 weeks*
- *≤ 36 weeks postpartum*
- *> 36 weeks postpartum, including women without recorded delivery within the past 52 weeks*

The crude incidence rate and 1- and 5-year cumulative incidence for IUD expulsion for postpartum timing of IUD insertion ≤ 3 days (newly added), > 3 days to ≤ 6 weeks (newly added), ≤ 6 weeks, > 6 to ≤ 14 weeks, > 14 to ≤ 52 weeks, > 52 weeks, ≤ 14 weeks, > 14 weeks, ≤ 36 weeks, and > 36 weeks are in Table 31, Figure 22, and Figure 23. The original plan was to have the earliest postpartum category in the multilevel analysis be ≤ 6 weeks, but in reviewing the data, we saw significant heterogeneity in that category, so we further divided that group into ≤ 3 days and 4 days to ≤ 6 weeks.

Table 31: Crude incidence rate (per 1,000 person-years) and cumulative incidence of IUD expulsion at 1 year and 5 years, first observed IUD insertions stratified by postpartum timing of IUD insertion; pooled and by research site

Research site and time postpartum	No. of insertions	Person-years	No. of events	Crude incidence rate (95% CI)	Crude cumulative incidence, 1 year (95 CI), %	Crude cumulative incidence, 5 years (95 CI), %
Pooled						
≤ 3 days	2,788	4,640.8	216	46.54 (40.54, 53.18)	7.84 (6.83, 9.00)	10.73 (9.12, 12.61)
4 days to ≤ 6 weeks	17,272	32,533.0	354	10.88 (9.78, 12.08)	1.61 (1.42, 1.84)	3.87 (3.40, 4.42)
≤ 6 weeks	20,060	37,173.8	570	15.33 (14.10, 16.65)	2.46 (2.24, 2.71)	4.81 (4.33, 5.33)
> 6 to ≤ 14 weeks	56,047	110,573.8	1,027	9.29 (8.73, 9.87)	1.40 (1.30, 1.51)	3.18 (2.95, 3.42)
> 14 to ≤ 52 weeks	21,717	40,676.0	584	14.36 (13.22, 15.57)	2.33 (2.12, 2.56)	4.55 (4.12, 5.02)
> 52 weeks or no delivery	228,834	453,003.7	6,762	14.93 (14.57, 15.29)	2.49 (2.42, 2.56)	4.88 (4.74, 5.02)

Research site and time postpartum	No. of insertions	Person-years	No. of events	Crude incidence rate (95% CI)	Crude cumulative incidence, 1 year (95 CI), %	Crude cumulative incidence, 5 years (95 CI), %
≤ 14 weeks	76,107	147,747.6	1,597	10.81 (10.29, 11.35)	1.68 (1.58, 1.78)	3.60 (3.39, 3.82)
> 14 weeks or no delivery	250,551	493,679.7	7,346	14.88 (14.54, 15.22)	2.48 (2.41, 2.55)	4.85 (4.72, 4.99)
≤ 36 weeks	91,869	177,534.7	2,029	11.43 (10.94, 11.94)	1.78 (1.69, 1.88)	3.81 (3.61, 4.02)
> 36 weeks or no delivery	234,789	463,892.5	6,914	14.90 (14.56, 15.26)	2.49 (2.42, 2.56)	4.86 (4.72, 4.99)
KPNC						
≤ 3 days	2,001	3,049.5	199	65.26 (56.50, 74.98)	10.05 (8.72, 11.58)	14.31 (11.91, 17.15)
4 days to ≤ 6 weeks	10,615	20,042.3	238	11.87 (10.41, 13.48)	1.66 (1.41, 1.95)	4.55 (3.88, 5.34)
≤ 6 weeks	12,616	23,091.8	437	18.92 (17.19, 20.78)	2.97 (2.66, 3.31)	6.04 (5.36, 6.81)
> 6 to ≤ 14 weeks	24,259	48,413.3	494	10.20 (9.32, 11.14)	1.49 (1.33, 1.67)	3.65 (3.28, 4.07)
> 14 to ≤ 52 weeks	9,056	16,870.2	299	17.72 (15.77, 19.85)	2.78 (2.43, 3.19)	5.78 (5.04, 6.62)
> 52 weeks or no delivery	115,511	237,176.2	3,805	16.04 (15.54, 16.56)	2.61 (2.51, 2.71)	5.51 (5.31, 5.72)
≤ 14 weeks	36,875	71,505.1	931	13.02 (12.20, 13.88)	1.99 (1.84, 2.15)	4.44 (4.10, 4.81)
> 14 weeks or no delivery	124,567	254,046.4	4,104	16.15 (15.66, 16.66)	2.62 (2.53, 2.72)	5.53 (5.33, 5.73)
≤ 36 weeks	43,175	83,358.1	1,149	13.78 (13.00, 14.60)	2.09 (1.95, 2.25)	4.71 (4.39, 5.06)
> 36 weeks or no delivery	118,267	242,193.4	3,886	16.05 (15.54, 16.56)	2.62 (2.52, 2.72)	5.49 (5.29, 5.70)
KPSC						
≤ 3 days	106	88.9	8	90.01 (38.86, 177.36)	8.00 (3.82, 16.35)	NE
4 days to ≤ 6 weeks	4,818	8,623.3	87	10.09 (8.08, 12.44)	1.69 (1.33, 2.15)	2.73 (2.15, 3.47)
≤ 6 weeks	4,924	8,712.2	95	10.90 (8.82, 13.33)	1.82 (1.45, 2.28)	2.89 (2.30, 3.63)
> 6 to ≤ 14 weeks	25,880	51,315.4	432	8.42 (7.64, 9.25)	1.32 (1.17, 1.48)	2.73 (2.44, 3.04)
> 14 to ≤ 52 weeks	10,265	19,180.0	227	11.84 (10.35, 13.48)	2.00 (1.72, 2.32)	3.45 (2.95, 4.03)
> 52 weeks or no delivery	82,145	162,715.7	2,418	14.86 (14.27, 15.46)	2.69 (2.57, 2.81)	4.47 (4.27, 4.69)
≤ 14 weeks	30,804	60,027.6	527	8.78 (8.05, 9.56)	1.40 (1.26, 1.55)	2.76 (2.50, 3.05)
> 14 weeks or no delivery	92,410	181,895.6	2,645	14.54 (13.99, 15.11)	2.61 (2.50, 2.72)	4.37 (4.18, 4.56)
≤ 36 weeks	38,495	74,501.8	692	9.29 (8.61, 10.01)	1.51 (1.38, 1.65)	2.90 (2.65, 3.16)
> 36 weeks or no delivery	84,719	167,421.4	2,480	14.81 (14.24, 15.41)	2.67 (2.55, 2.79)	4.45 (4.25, 4.65)

Research site and time postpartum	No. of insertions	Person-years	No. of events	Crude incidence rate (95% CI)	Crude cumulative incidence, 1 year (95 CI), %	Crude cumulative incidence, 5 years (95 CI), %
KPWA						
≤ 3 days	27	34.1	4	117.25 (31.95, 300.21)	12.21 (4.10, 33.29)	NE
4 days to ≤ 6 weeks	747	1,238.7	14	11.30 (6.18, 18.96)	1.68 (0.90, 3.15)	3.61 (1.74, 7.42)
≤ 6 weeks	774	1,272.8	18	14.14 (8.38, 22.35)	2.07 (1.20, 3.58)	4.32 (2.30, 8.05)
> 6 to ≤ 14 weeks	3,682	6,489.4	55	8.48 (6.38, 11.03)	1.29 (0.93, 1.79)	2.84 (1.96, 4.12)
> 14 to ≤ 52 weeks	1,369	2,484.1	36	14.49 (10.15, 20.06)	2.09 (1.39, 3.14)	5.89 (4.01, 8.60)
> 52 weeks or no delivery	14,701	27,249.9	327	12.00 (10.73, 13.37)	1.80 (1.58, 2.06)	4.26 (3.73, 4.86)
≤ 14 weeks	4,456	7,762.2	73	9.40 (7.37, 11.82)	1.43 (1.08, 1.89)	3.07 (2.24, 4.22)
> 14 weeks or no delivery	16,070	29,734.0	363	12.21 (10.98, 13.53)	1.83 (1.61, 2.08)	4.39 (3.87, 4.97)
≤ 36 weeks	5,483	9,658.5	104	10.77 (8.80, 13.05)	1.57 (1.24, 1.99)	3.90 (3.03, 5.01)
> 36 weeks or no delivery	15,043	27,837.7	332	11.93 (10.68, 13.28)	1.80 (1.58, 2.06)	4.21 (3.69, 4.80)
RI						
≤ 3 days	654	1,468.3	5	3.41 (1.11, 7.95)	0.70 (0.26, 1.85)	0.70 (0.26, 1.85)
4 days to ≤ 6 weeks	1,092	2,628.8	15	5.71 (3.19, 9.41)	0.80 (0.40, 1.60)	2.13 (1.12, 4.02)
≤ 6 weeks	1,746	4,097.1	20	4.88 (2.98, 7.54)	0.76 (0.43, 1.34)	1.61 (0.92, 2.82)
> 6 to ≤ 14 weeks	2,226	4,355.7	46	10.56 (7.73, 14.09)	1.53 (1.06, 2.22)	3.72 (2.57, 5.36)
> 14 to ≤ 52 weeks	1,027	2,141.7	22	10.27 (6.44, 15.55)	1.96 (1.23, 3.10)	2.91 (1.81, 4.66)
> 52 weeks or no delivery	16,477	25,861.9	212	8.20 (7.13, 9.38)	1.24 (1.06, 1.44)	2.30 (1.89, 2.80)
≤ 14 weeks	3,972	8,452.7	66	7.81 (6.04, 9.93)	1.19 (0.87, 1.62)	2.71 (2.01, 3.66)
> 14 weeks or no delivery	17,504	28,003.6	234	8.36 (7.32, 9.50)	1.28 (1.11, 1.48)	2.33 (1.94, 2.79)
≤ 36 weeks	4,716	10,016.3	84	8.39 (6.69, 10.38)	1.34 (1.02, 1.75)	2.83 (2.17, 3.68)
> 36 weeks or no delivery	16,760	26,440.0	216	8.17 (7.12, 9.33)	1.24 (1.07, 1.45)	2.27 (1.87, 2.76)

CI = confidence interval; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; NE = not estimable; RI = Regenstrief Institute.

Source: Analysis Tables 8.1 to 8.5.

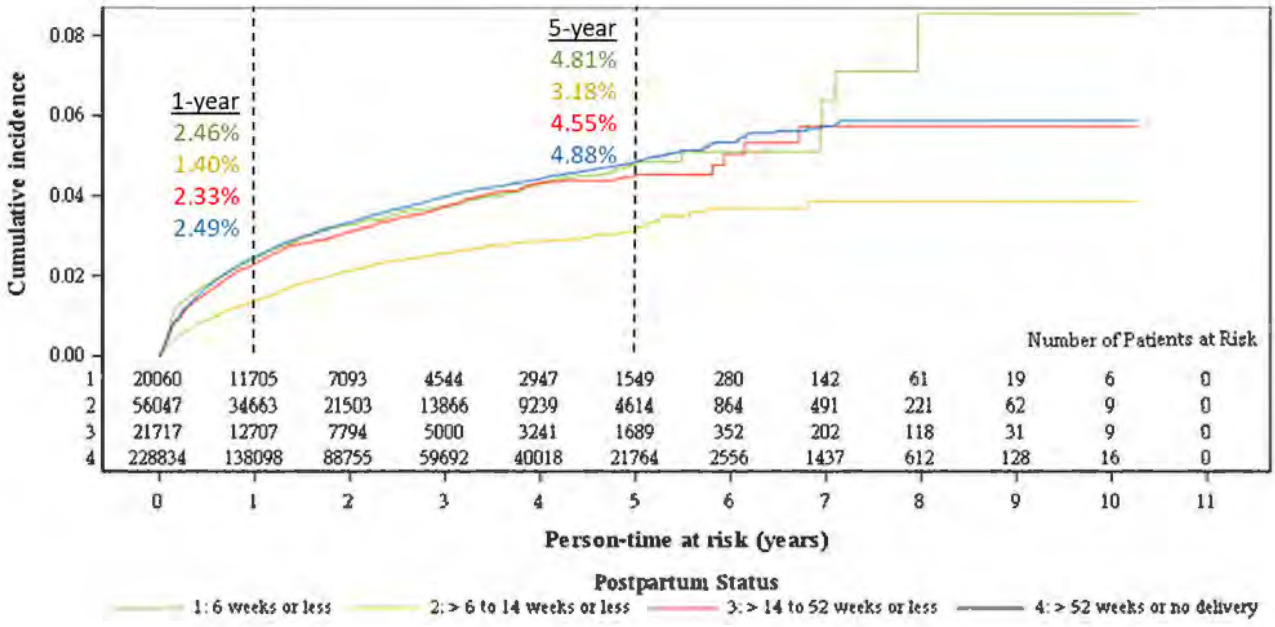


Figure 22: Crude cumulative incidence of IUD expulsion by 4-category postpartum timing of IUD insertion for the pooled study population (source: Analysis Table 8.1, Analysis Figure 9.1)

IUD = intrauterine device.

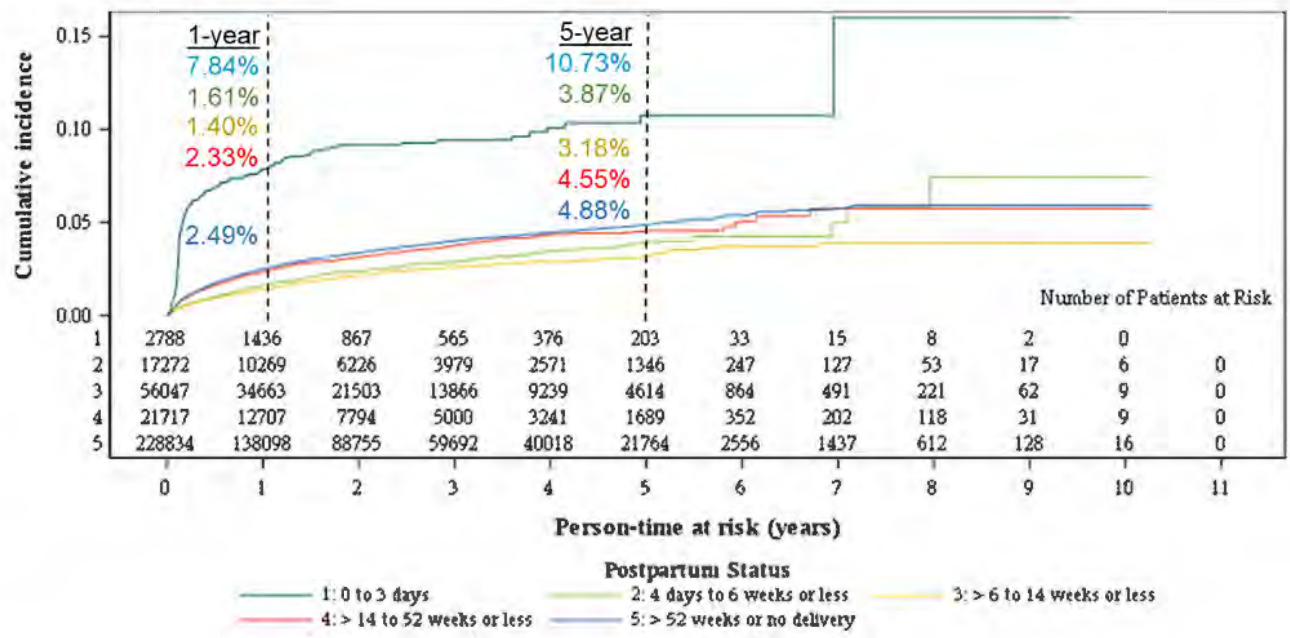


Figure 23: Crude cumulative incidence of IUD expulsion by 5-category postpartum timing of IUD insertion for the pooled study population (source: data from Additional Analysis Table 9.1, Additional Analysis Figure 9.2.1)

IUD = intrauterine device.

The crude incidence rates and cumulative incidence for IUD expulsion at 1 and 5 years in the original planned analysis were lowest for the group with IUD insertions > 6 to ≤ 14 weeks postpartum. We identified significant heterogeneity in the group ≤ 6 weeks postpartum, so we further stratified this group into the categories 0 to 3 days postpartum and 4 days to ≤ 6 weeks postpartum. With this additional stratification, the highest incidence of IUD expulsion was for the group with IUD insertions ≤ 3 days postpartum (pooled crude incidence, 46.54 expulsions per 1,000 person-years) and lowest in the postpartum insertion categories 4 days to ≤ 6 weeks (pooled crude incidence, 10.88 per 1,000 person-years) and > 6 to ≤ 14 weeks (pooled crude incidence, 9.29 per 1,000 person-years). In the dichotomous groupings with cut points at 14 and 36 weeks postpartum, the crude incidence rates and cumulative incidence for IUD expulsion at 1 and 5 years were lower in the earlier postpartum insertion groups (i.e., ≤ 14 weeks and ≤ 36 weeks); however, significant heterogeneity in these two categories, much as was seen for the multilevel analysis, is likely. These results are consistent across research sites except for RI, where the groups with IUD insertion ≤ 3 days, 4 days to ≤ 6 weeks, and ≤ 6 weeks had a lower incidence of IUD expulsion in the multilevel postpartum variables and the incidence was very similar in the early and later postpartum groups using the 14- and 36-week cut points.

10.5.6.2 IUD expulsion and postpartum timing risk, 14-week cut point—first observed IUD insertions (objective 21)

Objective 21: To estimate the adjusted hazard ratio of IUD expulsion among women who had a first observed IUD insertion early in the postpartum period (i.e., up to 14 weeks postpartum) versus those who had a first observed IUD insertion late in the postpartum period (i.e., more than 14 weeks postpartum, including women without recorded delivery within the past 52 weeks)

The crude, propensity score–adjusted, and fully adjusted HRs for IUD expulsion for IUD insertion ≤ 14 weeks postpartum versus > 14 weeks postpartum, for first IUD insertions, are shown in Figure 24, pooled and by research site.

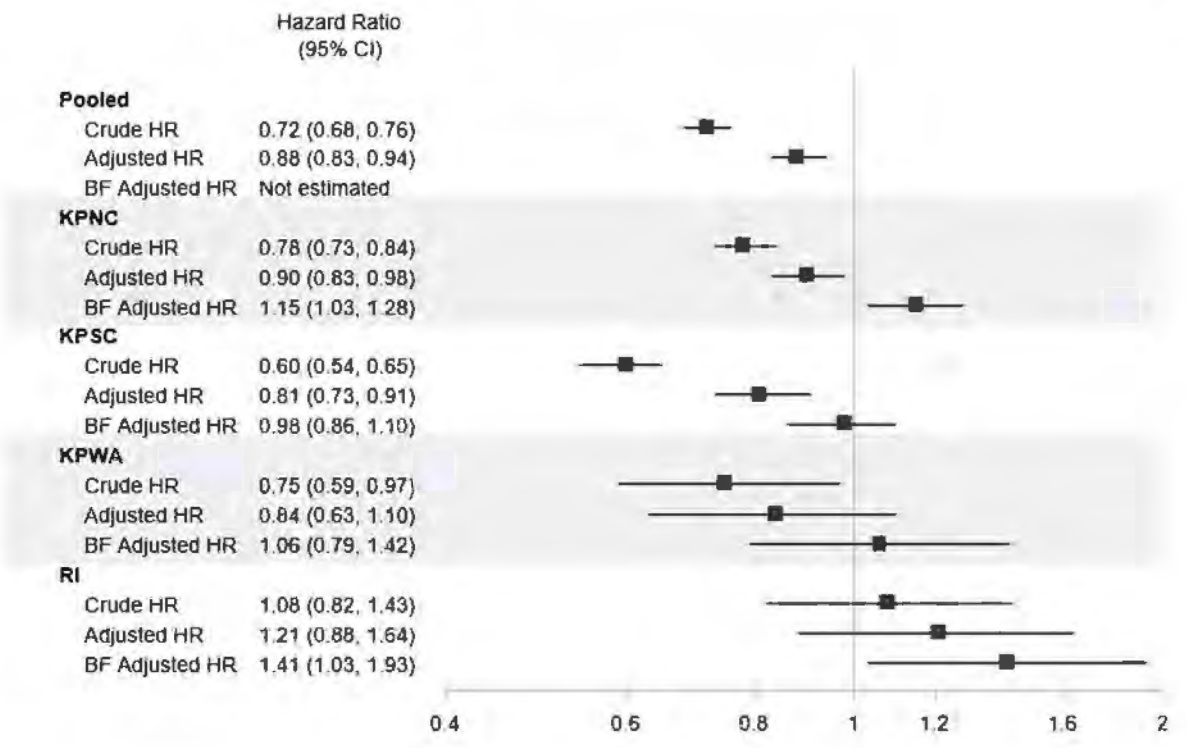


Figure 24: Crude, propensity score–adjusted, and fully adjusted hazard ratios for IUD expulsion for IUD insertion ≤ 14 weeks postpartum compared with those who had IUD insertion > 14 weeks postpartum or with no recorded delivery; pooled across sites and by research site, first observed IUD insertions (source: data from Analysis Table 21.1)

Adjusted HR = adjusted for propensity scores; BF Adjusted HR or fully adjusted = adjusted for propensity scores and breastfeeding status; CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute.

The complete study population was included in this analysis. The proportional hazards assumption was determined to be met based on visual inspection of the log-log survival curves. The same variables and propensity scores used in the 4-level postpartum timing/IUD expulsion propensity score model were used for this analysis. The propensity scores were collapsed into the relevant exposure groups to evaluate the distribution of the propensity scores across the dichotomous exposure groups before and after weighting (before weighting, Analysis Table 21.2; after weighting, Analysis Tables 21.3.1-21.3.5; and before and after weighting, Analysis Figures 21.1.1-21.1.5). Standardized differences prior to confounding adjustment were substantial, but after propensity score weighting, most of the variables included in the model had satisfactory balance (absolute standardized difference < 0.2). Among the variables included in propensity scores, the exceptions were race/ethnicity Hispanic other (KPSC) and BMI missing (KPWA), both of which were marginally unbalanced. Breastfeeding was not included in the propensity score model, but breastfeeding status was included as a covariate separate from the propensity score model.

The crude and propensity score–adjusted HRs for IUD expulsion were lower in the earlier postpartum group, defined as ≤ 14 weeks postpartum, compared with those with an IUD inserted > 14 weeks postpartum or with no recorded delivery (pooled crude HR, 0.72; adjusted HR, 0.88).

Propensity score adjustment attenuated the point estimates, and additional adjustment for breastfeeding status had a large impact—at KPNC the lower risk of IUD expulsion that was seen with postpartum IUD insertion ≤ 14 weeks in the crude and propensity score–adjusted estimates (crude HR, 0.78; adjusted HR, 0.90) changed to a higher risk of IUD expulsion when adjusting for breastfeeding status (fully adjusted HR, 1.15), and a similar directional shift occurred when adjusting for breastfeeding for all sites. Because of a significant site-by-exposure interaction (P = 0.0388, type 3 group test for statistical interaction), the breastfeeding adjustment was not applied for the pooled estimate.

10.5.6.3 IUD expulsion and postpartum timing risk 36 week cut point—first observed IUD insertions (objective 22)

Objective 22: To estimate the adjusted hazard ratio of IUD expulsion among women who had a first observed IUD insertion ≤ 36 weeks postpartum versus women who had a first observed IUD insertion > 36 weeks postpartum, including women without recorded delivery within the past 52 weeks

The crude, propensity score–adjusted, and fully adjusted HRs for IUD expulsion for IUD insertion ≤ 36 weeks postpartum versus > 36 weeks postpartum, first IUD insertion, are shown in Figure 25, pooled and by research site.

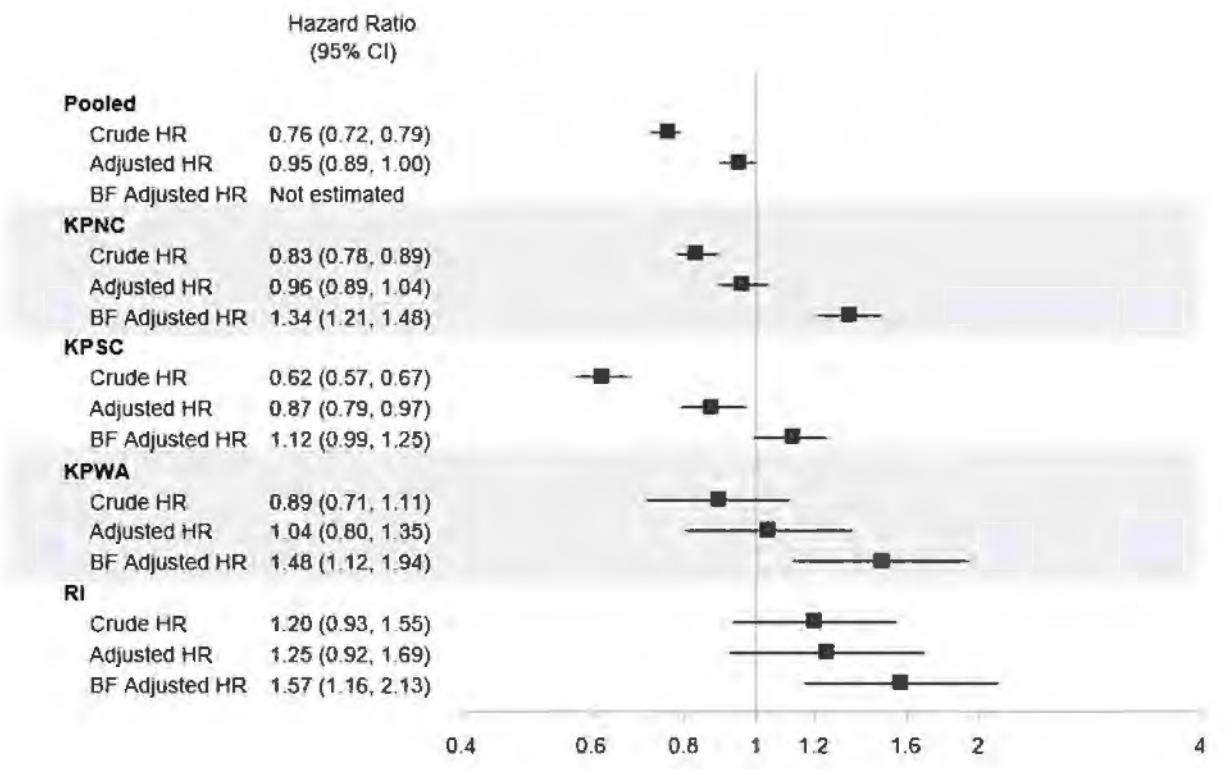


Figure 25: Crude, propensity score–adjusted, and fully adjusted hazard ratios for IUD expulsion for IUD insertion ≤ 36 weeks postpartum compared with > 36 weeks postpartum or with no recorded delivery; pooled across sites and by research site, first observed IUD insertions (source: data from Analysis Table 22.1)

Adjusted HR = adjusted for propensity scores; BF Adjusted HR or fully adjusted = adjusted for propensity scores and breastfeeding status; CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute.

The complete study population was included in this analysis. The proportional hazards assumption was determined to be met based on visual inspection of the curves. The same variables and propensity scores used in the 4-level postpartum timing/IUD expulsion propensity score model were used for this analysis. The propensity scores were collapsed into the relevant exposure groups to evaluate the distribution of the propensity scores across the dichotomous exposure groups before and after weighting (before weighting, Analysis Table 22.2; after weighting, Analysis Tables 22.3.1-22.3.5; before and after weighting, Analysis Figures 22.1.1-22.1.5). Standardized differences prior to confounding adjustment were substantial, but after propensity score weighting, most of the variables included in the model had satisfactory balance (absolute standardized difference < 0.2). Among the variables included in propensity scores, the exceptions were race/ethnicity Hispanic other (KPSC) and BMI missing (KPWA), both of which were marginally unbalanced. Breastfeeding was not included in the propensity score model, but breastfeeding status was included as a covariate separate from the propensity score model.

The crude and propensity score–adjusted HRs for IUD expulsion in the pooled data were somewhat lower in the earlier postpartum group, defined as ≤ 36 weeks, compared with IUD insertion > 36 weeks postpartum or with no recorded delivery (crude HR, 0.76; adjusted HR, 0.95). A similar

pattern was seen for KPNC and KPSC; the CIs were very wide for KPWA and RI. Propensity score adjustment attenuated the point estimates at all sites, and additional adjustment for breastfeeding status had a large impact—for all four sites, the risk of IUD expulsion for postpartum IUD insertion ≤ 36 weeks was higher after adjusting for breastfeeding status (although the lower limit of the 95% CI was 0.99 for KPSC). Because of a significant site-by-exposure interaction (P = 0.0114, type 3 group test for statistical interaction), the breastfeeding adjustment was not applied for the pooled estimate.

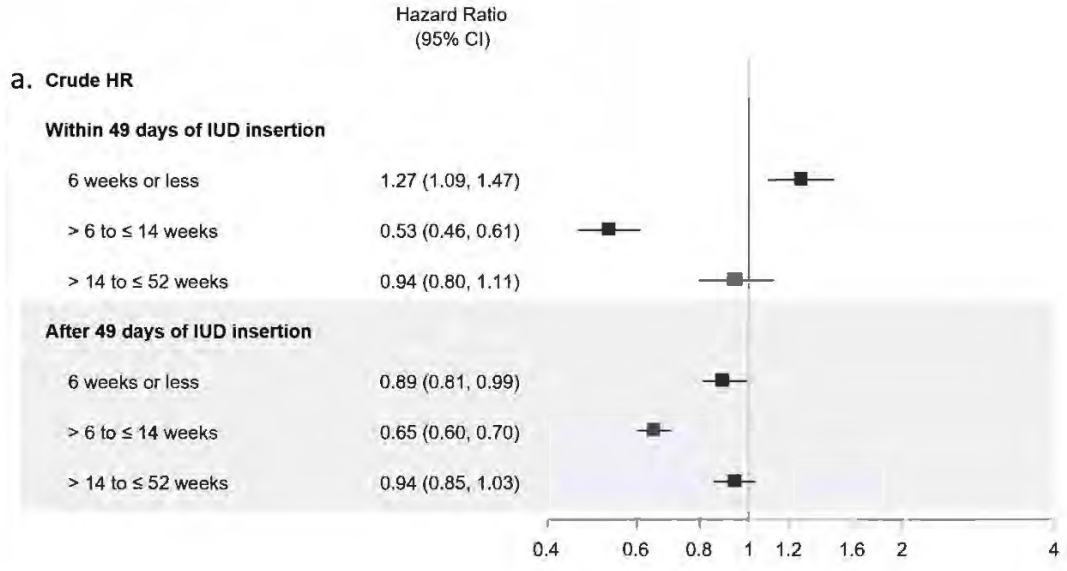
10.5.6.4 IUD expulsion and postpartum timing—first observed IUD insertions (objective 23 and additional analysis)

10.5.6.4.1 IUD expulsion and postpartum timing (4 categories)—first observed IUD insertions (objective 23)

Objective 23: To estimate the adjusted hazard ratios of IUD expulsion for women who had a first observed IUD insertion in early postpartum categories versus women who had a first observed IUD insertion late in the postpartum period, using the following strata:

- *≤ 6 weeks postpartum*
- *> 6 weeks and ≤ 14 weeks postpartum*
- *> 14 weeks and ≤ 52 weeks postpartum*
- *> 52 weeks postpartum, including women without recorded delivery in the past 52 weeks (referent category)*

The crude, propensity score–adjusted, and fully adjusted HRs for IUD expulsion using the four-category postpartum timing, for first IUD insertion, are shown in Figure 26 (pooled across research sites, stratified by follow-up time) and Figure 27 (by research site).



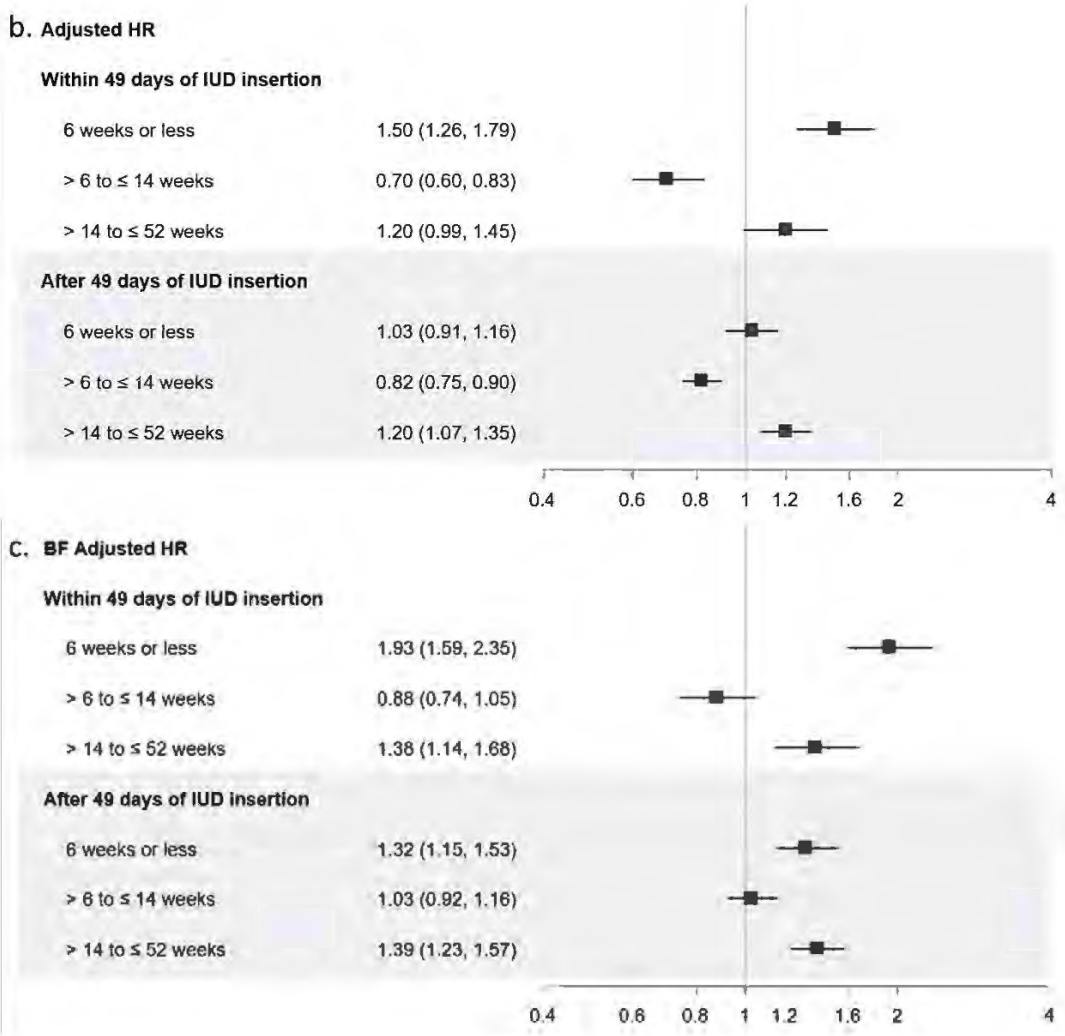


Figure 26: Crude (a), propensity score–adjusted (b), and fully adjusted (c) hazard ratios for IUD expulsion before and after 49 days after insertion for three categories of postpartum timing at IUD insertion, compared with those who were more than 52 weeks postpartum at IUD insertion or with no recorded delivery; pooled complete study population, first observed IUD insertions (source: data from Analysis Table 23.1a)

Adjusted HR = adjusted for propensity scores; BF Adjusted HR or fully adjusted = adjusted for propensity scores and breastfeeding status; CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute.

The complete study population was included in this analysis. The proportional hazards assumption was violated; therefore, a time-dependent interaction covariate, postpartum period by time (≤ 49 days from IUD insertion), was included in each Cox model. Prior to confounding adjustment, standardized differences were substantial (Analysis Table 23.2 and Analysis Figure 23.1.1 [pooled]; Analysis Table 23.2 and Analysis Figures 23.1.2-23.1.5 [each research site]). After propensity score weighting, most of the variables included in the model had satisfactory balance (absolute standardized difference < 0.2) (Analysis Tables 23.3.1-23.3.5 and Analysis Figures 23.1.1-23.1.5). Among the variables included in the propensity scores, the exceptions were race/ethnicity Hispanic other (KPSC), BMI missing (KPWA), and concomitant gynecological procedure (RI), all of which

were marginally unbalanced. Breastfeeding could not be included in the propensity score model because in the category > 52 weeks postpartum, no woman was categorized as breastfeeding at the time of IUD insertion; breastfeeding status was included as a covariate separate from the propensity score model.

In the crude and propensity score–adjusted analyses, the IUD insertion group > 6 weeks to ≤ 14 weeks postpartum had a lower risk of IUD expulsion than the group with IUDs inserted > 52 weeks postpartum or with no recorded delivery in both the ≤ 49 day postinsertion time period (crude, HR 0.53; adjusted HR, 0.70) and the > 49 day postinsertion time period (crude HR, 0.65; adjusted HR, 0.82). After additional adjustment for breastfeeding status at IUD insertion, the risk of IUD expulsion in the group with IUD insertion > 6 weeks to ≤ 14 weeks postpartum was no longer significantly lower in either follow-up time period (fully adjusted HR: ≤ 49 days, 0.88; > 49 days, 1.03). The risk of IUD expulsion in the group with IUD insertion > 6 weeks to ≤ 14 weeks postpartum was also lower than the other two early postpartum groups (≤ 6 weeks and > 14 to ≤ 52 weeks) in the crude, propensity score–adjusted, and fully adjusted analyses both within the first 49 days after insertion and after 49 days after insertion. Compared with the group with IUDs inserted > 52 weeks postpartum or with no recorded delivery, the risk of IUD expulsion within the first 49 days was highest in the group with IUDs inserted ≤ 6 weeks postpartum in the crude (HR, 1.27), propensity score–adjusted (HR, 1.50), and fully adjusted (HR, 1.93) analyses, and significantly higher than the comparator(> 52 weeks postpartum or with no recorded delivery) after the first 49 days only in the fully adjusted analysis (crude HR, 0.89; adjusted HR, 1.03; fully adjusted HR, 1.32). Propensity score adjustment tended to increase all the HR point estimates, and additional adjustment for breastfeeding increased the point estimates even more.

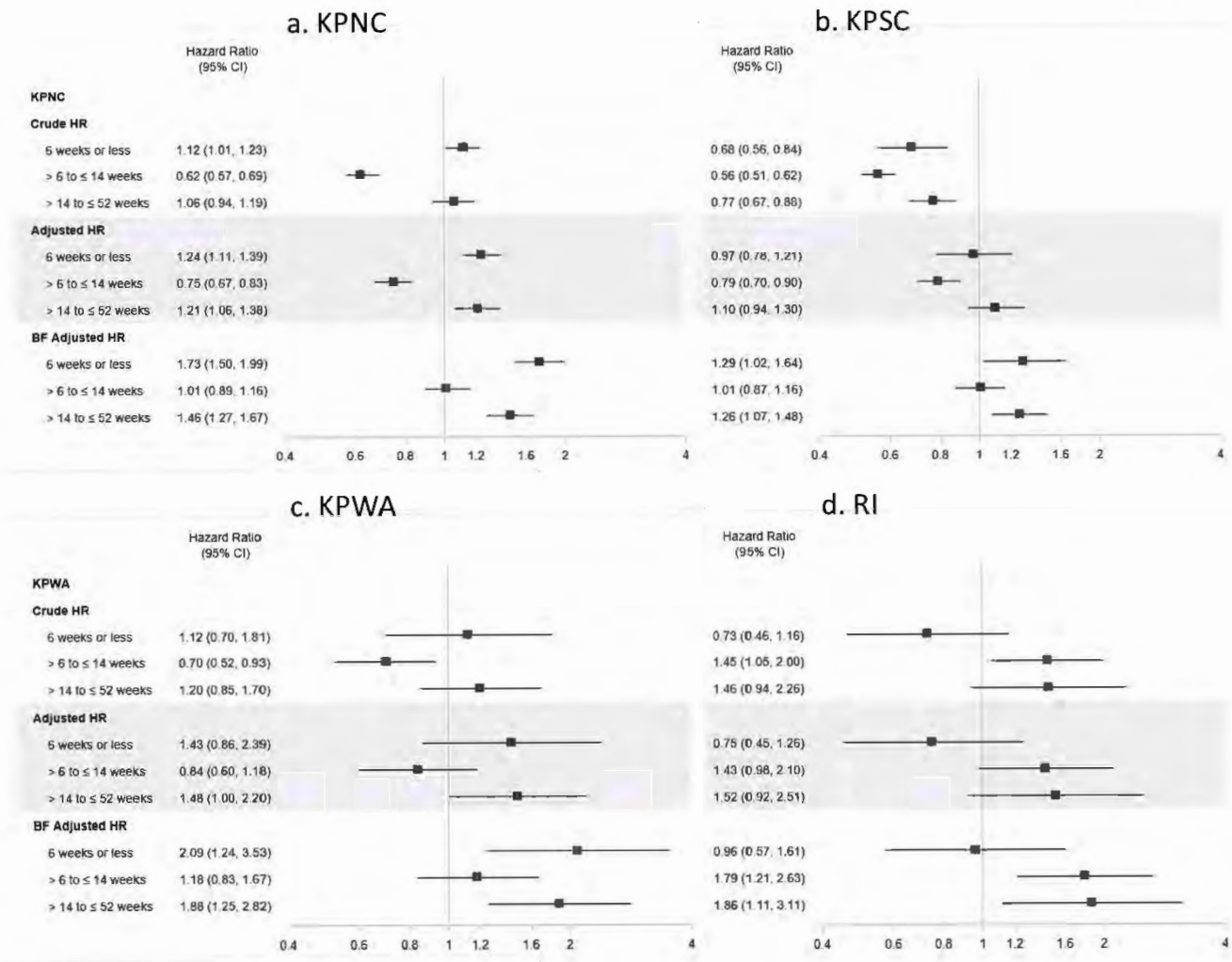


Figure 27: Crude, propensity score–adjusted, and fully adjusted hazard ratios for IUD expulsion for three categories of postpartum timing at IUD insertion compared with those who were more than 52 weeks postpartum at IUD insertion or with no recorded delivery, complete study population, first observed IUD insertions; a. KPNC, b. KPSC, c. KPWA, d. RI (source: fig_table_23_01_1_KPNC[_2_KPSC, _3_KPWA, _4_RI].svg,)

Adjusted HR = adjusted for propensity scores; BF Adjusted HR or fully adjusted = adjusted for propensity scores and breastfeeding status; CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute.

In the site-specific analyses, the pattern of the group with IUD insertion > 6 weeks to ≤ 14 weeks postpartum having a lower risk of IUD expulsion than the other two early postpartum groups was evident at KPNC, KPSC, and KPWA. At RI, the lowest risk of IUD expulsion among the three early postpartum IUD insertion groups was in the group with IUD insertion ≤ 6 weeks postpartum. The effect of adjustment for propensity scores or for propensity scores and breastfeeding status was also the same for each research site as for the pooled analysis, tending to shift the point estimates toward a higher risk of IUD expulsion in the early postpartum insertion groups than in the later IUD insertion groups. At all four research sites, after adjustment for propensity scores and breastfeeding status, the risk of IUD expulsion was significantly higher in the group with IUD insertion ≤ 6 weeks

postpartum and the group with IUD insertion > 14 to ≤ 52 weeks postpartum compared with the comparator (IUD insertion > 52 weeks postpartum or with no recorded delivery).

10.5.6.4.2 IUD expulsion and postpartum timing (5 categories)—first observed IUD insertions (additional analysis)

The crude, propensity score–adjusted, and fully adjusted HRs for IUD expulsion using five-category postpartum timing, for first IUD insertion, are shown in Figure 28.

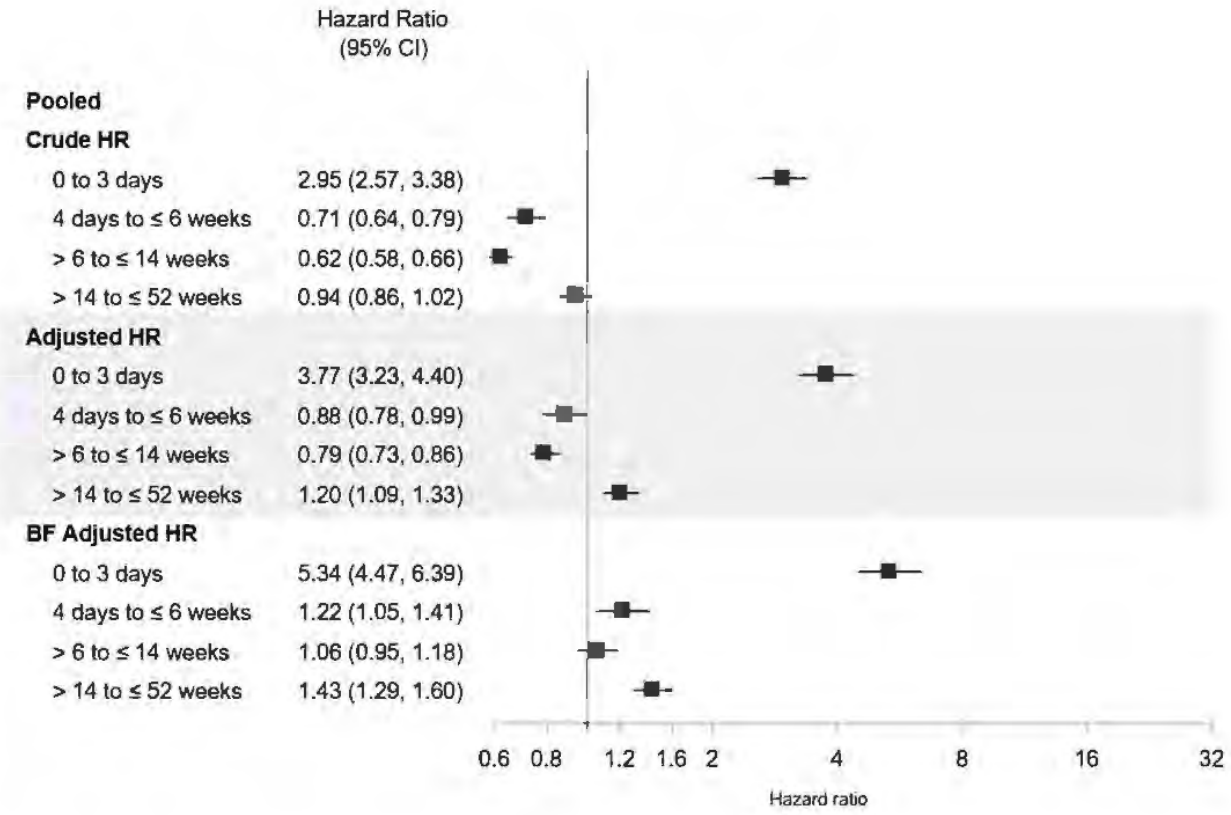


Figure 28: Crude, propensity score–adjusted, and fully adjusted hazard ratios for IUD expulsion for four categories of postpartum timing at IUD insertion compared with those who were more than 52 weeks postpartum or with no recorded delivery; pooled complete study population, first observed IUD insertions (source: fig_PPCat5_HR_35_2.svg)

Adjusted HR = adjusted for propensity scores; BF Adjusted HR or fully adjusted = adjusted for propensity scores and breastfeeding status; CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.

The complete study population was included in this analysis. The same propensity score weighting as was used in the 4-level postpartum timing analysis was used in this analysis. In the crude and propensity score–adjusted analyses, the group with IUD insertion 0 to 3 days postpartum had a higher risk of IUD expulsion (crude HR, 2.95; adjusted HR, 3.77) and the group with IUD insertion 4 days to ≤ 6 weeks postpartum (crude HR, 0.71; adjusted HR, 0.88) and group with IUD insertion > 6 weeks to ≤ 14 weeks postpartum (crude HR, 0.62; adjusted HR, 0.79) had a lower risk of IUD expulsion than the group with IUDs inserted > 52 weeks postpartum or with no recorded delivery. After additional adjustment for breastfeeding status at IUD insertion, the point estimates for all postpartum timing groups shifted to the right (in the direction of higher risk); the group with IUD

insertion 0 to 3 days postpartum still had the highest risk of IUD expulsion (fully adjusted HRs: 0 to 3 days, 5.34; 4 days to ≤ 6 weeks, 1.22; > 6 to ≤ 14 weeks, 1.06; > 14 to ≤ 52 weeks, 1.43).

10.5.6.5 IUD expulsion and postpartum timing, incidence rate ratios and differences, 36-week cut point—first observed IUD insertions (objective 25)

Objective 25: To estimate the adjusted incidence rate ratio (IRR) and incidence rate difference (IRD) of IUD expulsion at 1 year and 5 years of follow-up among women who had a first observed IUD insertion ≤ 36 weeks postpartum versus women who had a first observed IUD insertion > 36 weeks postpartum, including women without recorded delivery within the past 52 weeks

The crude incidence rates and crude and propensity score–adjusted IRRs, stratified by breastfeeding status, were estimated for IUD expulsion with postpartum timing of first IUD insertion ≤ 36 weeks versus > 36 weeks or no recorded delivery. Pooled results are shown in Table 32 and Figure 29. The IRDs pooled across all sites are shown in Table 33. The complete study population was included in this analysis. Adjustment was done via weighted estimation of the rates using overlap weights derived from the same propensity score models as those developed for adjustment of the HRs for the 36-week cut point.

Table 32: Number or events, person-time of follow-up, and crude incidence rates (per 1,000 person-years) of IUD expulsion for ≤ 36 weeks postpartum at IUD insertion and > 36 weeks postpartum or with no recorded delivery, 1 year of follow-up and 5 years of follow-up, overall and stratified by breastfeeding status; complete study population, pooled across research sites, first observed IUD insertions

Breastfeeding status	Measure	1 year of follow-up		5 years of follow-up	
		≤ 36 weeks	> 36 weeks or no delivery	≤ 36 weeks	> 36 weeks or no delivery
Overall	No. of events	1,383	4,953	2,006	6,865
	Person-years	71,595.2	182,233.7	172,863.3	453,355.2
	Crude incidence rate	19.32	27.18	11.60	15.14
Yes	No. of events	813	32	1,220	36
	Person-years	49,483.8	1,178.7	118,178.2	2,708.0
	Crude incidence rate	16.43	27.15	10.32	13.29
No	No. of events	541	4,915	743	6,820
	Person-years	20,209.5	180,715.9	50,080.3	449,784.8
	Crude incidence rate	26.77	27.20	14.84	15.16
Undetermined	No. of events	29	6	43	9
	Person-years	1,901.9	339.1	4,604.8	862.4
	Crude incidence rate	15.25	17.69	9.34	10.44

IUD = intrauterine device.
Source: Analysis Tables 25.1 through 25.5 (pooled and by research site).

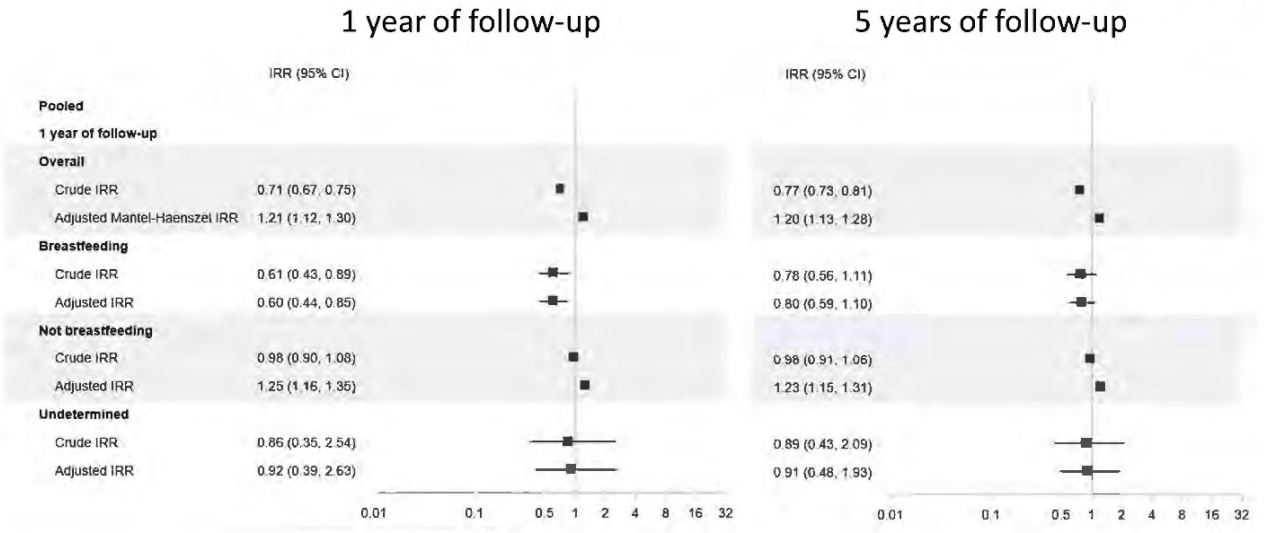


Figure 29: Crude and adjusted incidence rate ratios (overall and stratified by breastfeeding status at the time of IUD insertion) for IUD expulsion for ≤ 36 weeks postpartum at IUD insertion compared with those who were more than 36 weeks postpartum or with no recorded delivery at 1 year of follow-up and 5 years of follow-up; pooled across research sites, complete study population, first observed IUD insertions (source: data from Analysis Tables 25.1 through 25.5, pooled and by research site)

CI = confidence interval; IRR = incidence rate ratio; IUD = intrauterine device.

The crude incidence rates are in Table 33, and the crude incidence rate of IUD expulsion in the overall and breastfeeding groups who were > 36 weeks postpartum at the time of IUD insertion were approximately 40% to 65% higher than in the groups who were ≤ 36 weeks postpartum at IUD insertion. For the group that was not breastfeeding, the crude incidence rates in the two postpartum strata were very similar. In the overall IRR estimates at 1 and 5 years of follow-up, risk of IUD expulsion was lower in the earlier postpartum group (≤ 36 weeks) than in those with an IUD inserted > 36 weeks postpartum or with no recorded delivery in the crude analysis (1-year IRR, 0.71; 5-year IRR, 0.77), and the risk was higher than the comparator group in the adjusted analysis (1-year IRR, 1.21; 5-year IRR, 1.20). There was a lower risk of IUD expulsion with earlier postpartum IUD insertion among those who were breastfeeding at the time of IUD insertion at 1 year (adjusted IRR, 0.60), but the CI included the null value at 5 years (adjusted IRR, 0.80). There was a higher risk of IUD expulsion in the earlier postpartum insertion group (after adjustment) among those who were not breastfeeding at the time of IUD insertion at both the 1- and 5-year follow-up times (adjusted 1-year IRR, 1.25; adjusted 5-year IRR, 1.23).

Table 33: Crude and adjusted[a] incidence rate differences (per 1,000 person-years) for IUD expulsion for ≤ 36 weeks postpartum at IUD insertion compared with those who were more than 36 weeks postpartum or with no recorded delivery at 1 year of follow-up and 5 years of follow-up, overall and stratified by breastfeeding status; complete study population pooled across research sites, first observed IUD insertions

Breast-feeding status	Statistic	1 year of follow-up		5 years of follow-up	
		≤ 36 weeks	> 36 weeks or no delivery	≤ 36 weeks	> 36 weeks or no delivery
Overall	Crude IRD	−7.86 (−9.13, −6.59)	Reference	−3.54 (−4.16, −2.92)	Reference
	Adjusted IRD[b]	4.28 (2.50, 6.06)	Reference	2.37 (1.53, 3.22)	Reference
Yes	Crude IRD	−10.72 (−20.19, −1.24)	Reference	−2.97 (−7.35, 1.41)	Reference
	Adjusted IRD	−10.79 (−19.43, −2.15)	Reference	−2.62 (−6.51, 1.26)	Reference
No	Crude IRD	−0.43 (−2.81, 1.95)	Reference	−0.33 (−1.45, 0.80)	Reference
	Adjusted IRD	5.11 (3.27, 6.94)	Reference	2.65 (1.78, 3.53)	Reference
Undeter-mined	Crude IRD	−2.44 (−17.65, 12.76)	Reference	−1.10 (−8.46, 6.27)	Reference
	Adjusted IRD	−1.27 (−14.38, 11.84)	Reference	−0.92 (−7.49, 5.65)	Reference

CI = confidence interval; IRD = incidence rate difference; IUD = intrauterine device.
[a] Adjusted via weighted estimation of the rates using overlap weights derived from the same propensity score models as those developed for adjustment of the hazard ratios.
[b] Mantel-Haenszel estimate.
Source: Analysis Tables 25.1 through 25.5 (pooled and by research site).

The incidence rate differences showed a similar pattern to the IRRs, with overall an additional 4.3 IUD expulsions per 1,000 person-years in the early postpartum insertion group compared with the later postpartum insertion group at 1 year and 2.4 additional expulsions per 1,000 person-years at 5 years of follow-up. The estimates for those with earlier postpartum timing who were not breastfeeding were 5.1 additional IUD expulsions per 1,000 person-years at 1 year and 2.7 additional expulsions per 1,000 person-years at 5 years. Among those who were breastfeeding, earlier postpartum timing was associated with a significantly lower number of expulsions at 1 year (10.8 per 1,000 person-years), and that difference was attenuated by 5 years of follow-up.

10.5.7 IUD expulsion and breastfeeding—first observed IUD insertions (objectives 10, 20)

10.5.7.1 IUD expulsion and breastfeeding, incidence—first observed IUD insertions (objective 10)

Objective 10: To estimate the incidence rate and cumulative incidence of IUD expulsion among women who were and were not breastfeeding at the time of IUD insertion

The crude incidence rate and 1- and 5-year cumulative incidence for IUD expulsion by breastfeeding status at the time of IUD insertion are shown in Table 34. Figure 30 displays the cumulative incidence of IUD expulsion over follow-up time stratified by breastfeeding status at the time of IUD insertion.

Table 34: Crude incidence rate (per 1,000 person-years) and cumulative incidence of IUD expulsion at 1 year and 5 years, stratified by breastfeeding status; pooled and by research site, first observed IUD insertions

Research site and breast-feeding status	No. of insertions	Person-years	No. of events	Crude incidence rate (95% CI)	Crude cumulative incidence, 1 year (95 CI), %	Crude cumulative incidence, 5 years (95 CI), %
Pooled						
Breastfeeding	64,186	123,902.8	1,268	10.23 (9.68, 10.81)	1.55 (1.44, 1.65)	3.49 (3.25, 3.73)
Not breastfeeding	30,631	58,835.6	858	14.58 (13.62, 15.59)	2.45 (2.27, 2.65)	4.57 (4.22, 4.95)
Undetermined	3,007	5,685.1	55	9.67 (7.29, 12.59)	1.43 (1.02, 1.99)	3.00 (2.21, 4.05)
KPNC						
Breastfeeding	34,357	66,888.5	868	12.98 (12.13, 13.87)	1.98 (1.83, 2.15)	4.43 (4.08, 4.81)
Not breastfeeding	10,996	20,500.0	347	16.93 (15.19, 18.80)	2.70 (2.38, 3.06)	5.58 (4.88, 6.36)
Undetermined	578	986.8	15	15.20 (8.51, 25.07)	1.81 (0.94, 3.47)	5.00 (2.80, 8.85)
KPSC						
Breastfeeding	23,679	45,533.8	299	6.57 (5.84, 7.35)	0.96 (0.83, 1.10)	2.17 (1.90, 2.49)
Not breastfeeding	17,027	32,937.2	452	13.72 (12.49, 15.05)	2.41 (2.17, 2.68)	4.03 (3.63, 4.48)
Undetermined	363	736.5	3	4.07 (0.84, 11.90)	0.62 (0.15, 2.45)	1.27 (0.38, 4.20)
KPWA						
Breastfeeding	3,964	7,296.9	62	8.50 (6.51, 10.89)	1.30 (0.96, 1.76)	2.97 (2.11, 4.19)
Not breastfeeding	875	1,544.8	30	19.42 (13.10, 27.72)	2.97 (1.94, 4.55)	6.79 (4.50, 10.19)
Undetermined	986	1,404.6	17	12.10 (7.05, 19.38)	1.57 (0.83, 2.95)	4.65 (2.57, 8.34)
RI						
Breastfeeding	2,186	4,183.5	39	9.32 (6.63, 12.74)	1.50 (1.03, 2.18)	3.15 (2.13, 4.64)
Not breastfeeding	1,733	3,853.6	29	7.53 (5.04, 10.81)	1.08 (0.66, 1.77)	2.80 (1.77, 4.43)
Undetermined	1,080	2,557.3	20	7.82 (4.78, 12.08)	1.45 (0.86, 2.45)	2.07 (1.30, 3.29)

CI = confidence interval; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute.
Source: Analysis Tables 8.1 to 8.5.

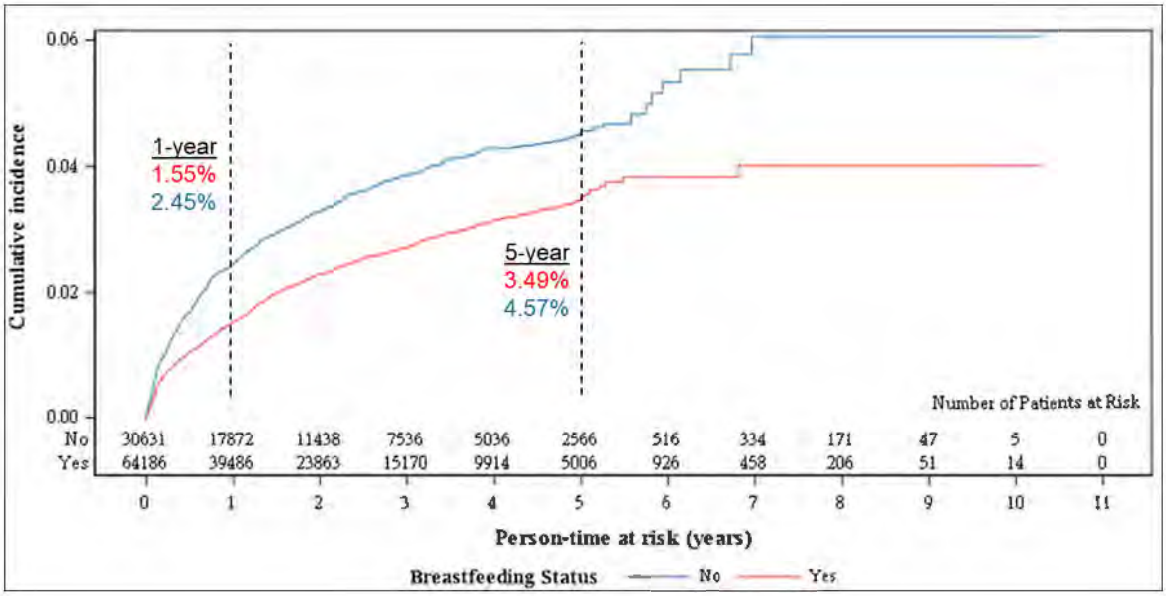


Figure 30: Crude cumulative incidence of IUD expulsion by breastfeeding status for the pooled study population (source: data from Analysis Table 8.1, Analysis Figure 10.1)

IUD = intrauterine device.

The crude incidence rates and cumulative incidence for IUD expulsion at 1 and 5 years were lower among women who were breastfeeding at the time of IUD insertion (pooled crude incidence, 10.23 per 1,000 person-years) versus those not breastfeeding (pooled crude incidence, 14.58 per 1,000 person-years), overall and across all research sites except RI. IUD expulsion among those with undetermined breastfeeding status was variable, with rates between those breastfeeding and not breastfeeding for three sites and lower rates than any known breastfeeding status at the remaining site (KPSC).

10.5.7.2 IUD expulsion and breastfeeding—first observed IUD insertions (objective 20)

Objective 20: To estimate the adjusted hazard ratio of IUD expulsion among women who were breastfeeding at the time of first observed IUD insertion versus those who were not breastfeeding at the time of first observed IUD insertion

The crude and propensity score–adjusted HRs for IUD expulsion and breastfeeding status for the first IUD insertion were estimated. Pooled results are displayed in Figure 31.

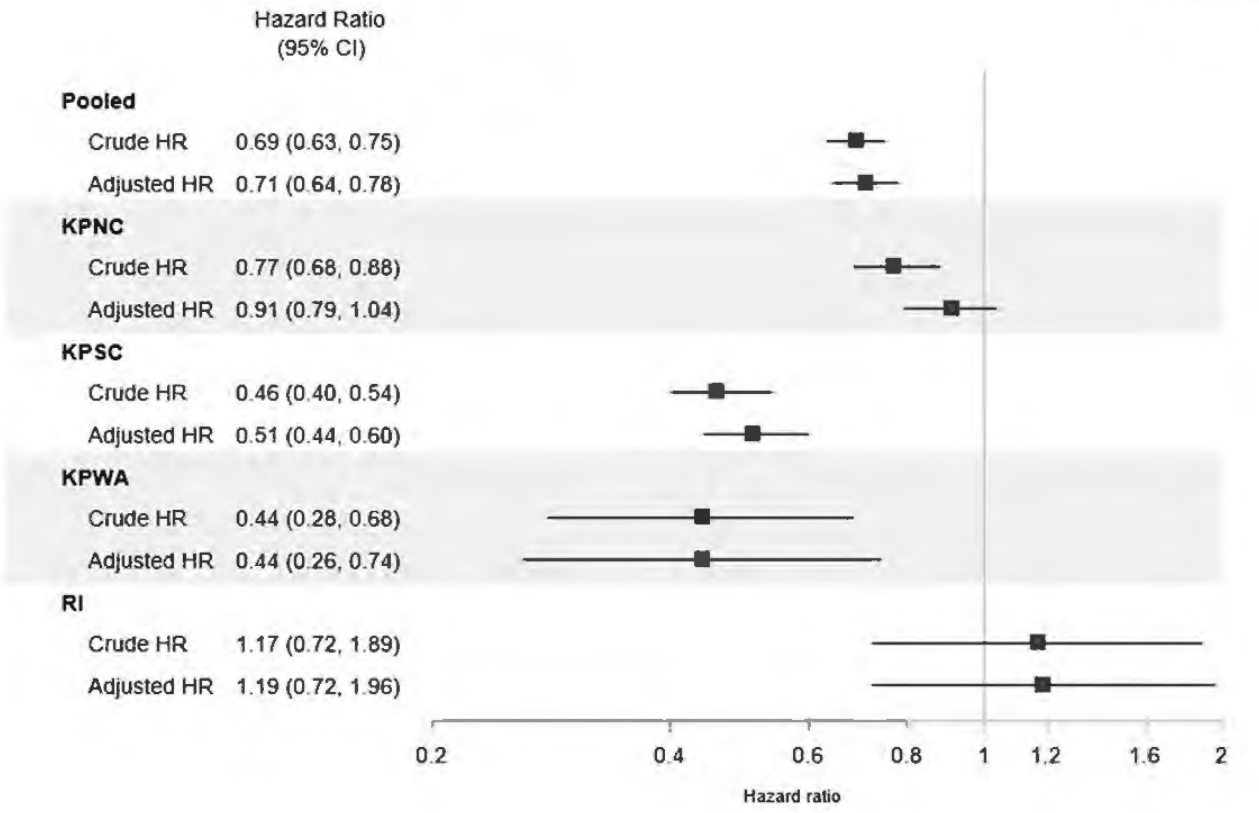


Figure 31: Crude and propensity score–adjusted hazard ratios for IUD expulsion for women breastfeeding at the time of IUD insertion compared with women who were not breastfeeding at time of IUD insertion; pooled and by site, population of women giving birth within the previous 52 weeks, first observed IUD insertions (source: data from Analysis Table 20.1, pooled and by research site)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute

Only those women who had given birth in the previous 52 weeks were included in this analysis. In crude analyses, women who were breastfeeding at the time of IUD insertion were less likely to have IUD expulsion than women who were not breastfeeding. The proportional hazards assumption was satisfied through 5 years after insertion. Standardized differences prior to confounding adjustment were substantial (pooled: Analysis Table 1.2.1; by site: Analysis Tables 1.2.2-1.2.5). After propensity score weighting using initial propensity score models, all levels of variables had satisfactory balance in the pooled data (absolute standardized difference < 0.2), and most were satisfactory at all sites (Analysis Tables 20.3.1-20.3.5 and Analysis Figures 20.1.1-20.1.5). The exceptions were calendar year of index (2001-2009) at KPWA and RI, postpartum status ≤ 6 weeks at KPWA, and postpartum status > 14 to ≤ 52 weeks at KPWA and RI. An interaction term by site was included for the four-level postpartum status variable. After inclusion of this interaction term, all levels of variables had satisfactory balance in the pooled data and were either satisfactory or attenuated at each site. The levels with absolute standardized differences that were less well balanced were calendar year of index date (2001-2009) at KPWA and RI and race/ethnicity non-Hispanic white at RI (absolute standardized difference for all were 0.2-0.3).

The pooled adjusted HR for IUD expulsion was 0.71 for the comparison of those who were breastfeeding versus those who were not breastfeeding at the time of IUD insertion. There was a statistically significant interaction between breastfeeding status and research site. At KPSC and KPWA, after adjustment, women who were breastfeeding at the time of IUD insertion remained less likely to have IUD expulsion than women who were not breastfeeding (adjusted HR: KPSC, 0.51; KPWA, 0.44). At KPNC, the point estimate suggested a slightly lower risk of IUD expulsion among women who were breastfeeding (adjusted HR, 0.91), but the 95% CI included the null value. At RI, the adjusted HR point estimate was 1.19. Adjustment for confounding via propensity scores increased the HRs at all sites, which was toward the null except at RI. These HRs are consistent with the trends in crude incidence and cumulative incidence.

10.5.8 IUD expulsion and IUD type—first observed IUD insertions (objectives 11, 24)

10.5.8.1 IUD expulsion and IUD type, incidence—first observed IUD insertions (objective 11)

Objective 11: To estimate the incidence rate and cumulative incidence of IUD expulsion among women with different types of IUD (i.e., LNG-IUD and copper IUD)

The crude incidence rate and 1- and 5-year cumulative incidence for IUD expulsion by IUD type (LNG, copper, unknown) are shown in Table 35 and Figure 32. Data are not presented by research site in compliance with the Kaiser Permanente Data Use Agreement.

Table 35: Crude incidence rate (per 1,000 person-years) and cumulative incidence of IUD expulsion at 1 year and 5 years, first observed IUD insertions stratified by IUD type; pooled across research sites

IUD type	No. of insertions	Person-years	No. of events	Crude incidence rate (95% CI)	Crude cumulative incidence, 1 year (95 CI), %	Crude cumulative incidence, 5 years (95 CI), %
LNG-IUD	259,234	507,151.2	7,075	13.95 (13.63, 14.28)	2.30 (2.24, 2.36)	4.52 (4.40, 4.65)
Copper	63,664	127,587.0	1,797	14.08 (13.44, 14.75)	2.30 (2.18, 2.44)	4.82 (4.56, 5.10)
Unknown	3,760	6,689.1	71	10.61 (8.29, 13.39)	1.55 (1.16, 2.07)	3.75 (2.81, 5.00)

CI = confidence interval; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.
Source: Analysis Tables 8.1 to 8.5.

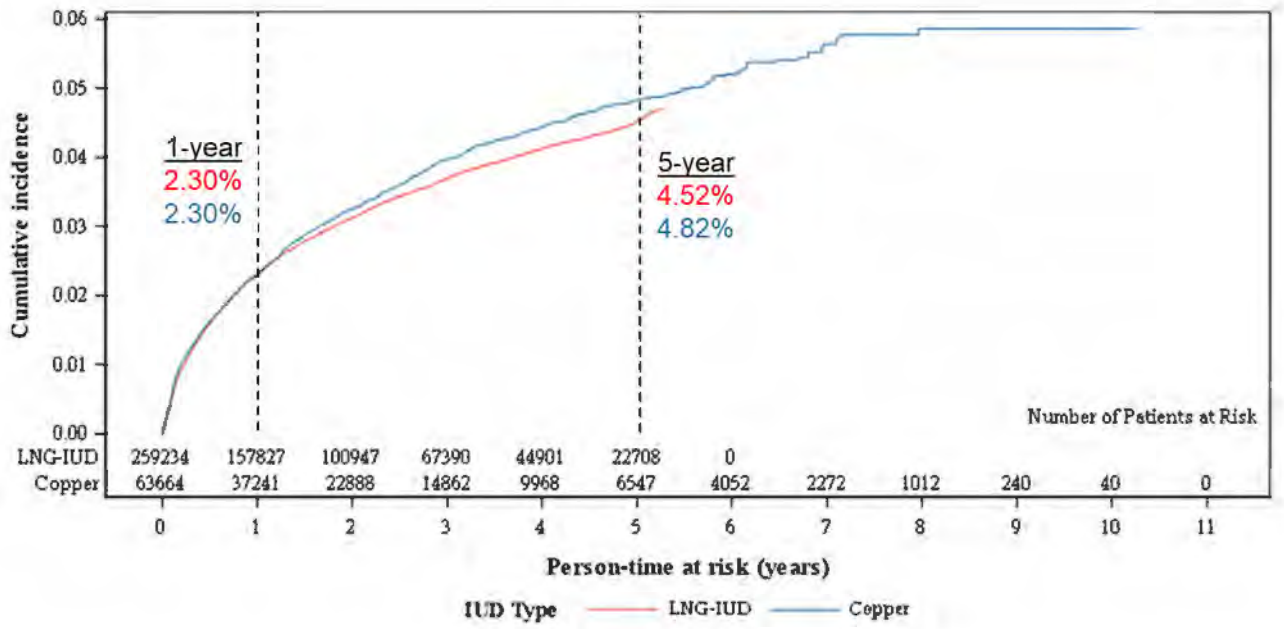


Figure 32: Crude cumulative incidence of IUD expulsion pooled across sites by IUD type (source: data from Analysis Table 8.1, Analysis Figure 11.1)

IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system

The crude incidence rate and cumulative incidence for IUD expulsion at 1 and 5 years were very similar among those with LNG-IUDs and copper IUDs (crude incidence rate: LNG, 13.95; copper, 14.08). Labeled IUD expiration was used as a censoring event for these analyses; as can be seen in Figure 32, there is an increase in the number of LNG-IUD expulsions right around 5 years after IUD insertion, which likely reflects the IUD expulsions that were recognized at the time the woman returned to have the IUD removed for those IUDs with a 5-year expiration. This trend is not seen around the 10-year expiration for copper IUDs because only two sites had the potential for 10 years of follow-up, and the sample size dropped rapidly after 6 years of follow-up.

10.5.8.2 IUD expulsion and IUD type, risk—first observed IUD insertions (objective 24)

Objective 24: To estimate the adjusted hazard ratio of IUD expulsion for women whose first observed IUD was an LNG-releasing IUD versus women whose first observed IUD was a copper IUD

The crude and propensity score–adjusted HRs for IUD expulsion for the comparison of LNG-IUDs to copper IUDs, for first IUD insertions, are shown in Figure 33, pooled across research sites.

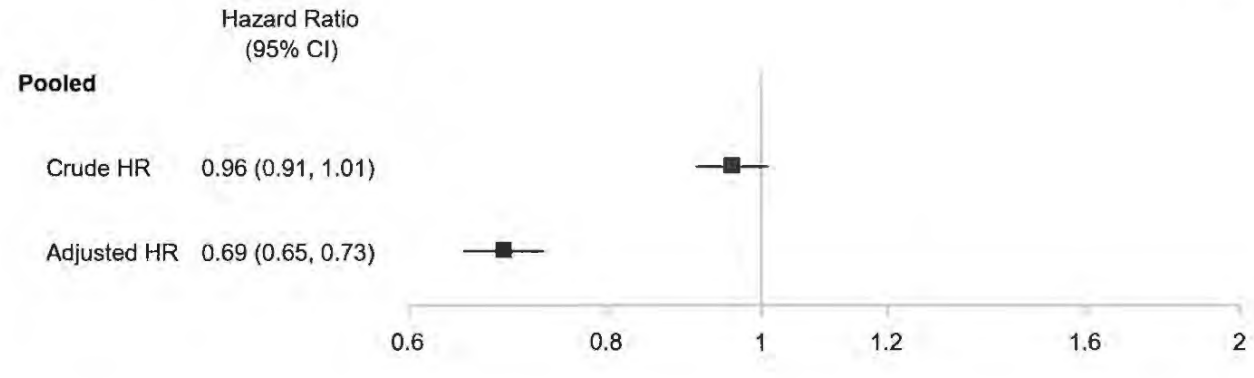


Figure 33: Crude and propensity score–adjusted hazard ratios for IUD expulsion for LNG-IUDs compared with copper IUDs; pooled across sites, first observed IUD insertions (source: data from Analysis Table 24.1)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.

The study population with IUD type available is included for this analysis (i.e., those with unknown IUD type were excluded). The proportional hazards assumption was satisfied. Standardized differences prior to confounding adjustment were modest, i.e., only one variable with a value > 0.2 (Analysis Table 24.2.1 and Analysis Figure 24.1.1). After propensity score weighting, all of the variables included in the model had satisfactory balance (absolute standardized difference < 0.2) (Analysis Table 24.3.1 and Analysis Figure 24.1.1).

The risk of IUD expulsion was marginally lower for LNG-IUDs than for copper IUDs before adjustment (crude HR, 0.96) and significantly lower after propensity score adjustment (adjusted HR, 0.69).

10.5.9 IUD expulsion and menorrhagia—first observed IUD insertions (objectives 12, 27)

10.5.9.1 IUD expulsion and menorrhagia, incidence—first observed IUD insertions (objective 12: complete study population [per protocol] and excluding those with a delivery in the previous 52 weeks [additional analysis])

Objective 12: To estimate the incidence rate and cumulative incidence of IUD expulsion among women with and without menorrhagia in the 12 months before IUD insertion

The crude incidence rate and 1- and 5-year cumulative incidence for IUD expulsion by menorrhagia status for the complete study population (per protocol) and for the study population of women who were more than 52 weeks postpartum at IUD insertion or with no recorded delivery, including nulliparous women (additional analysis) are shown in Table 36. Figure 34 (complete study population) and Figure 35 (among those without a delivery in the previous 52 weeks) show the cumulative incidence of IUD expulsion stratified by whether the woman had a diagnosis of menorrhagia in the year prior to IUD insertion.

Table 36: Crude incidence rate (per 1,000 person-years) and cumulative incidence of IUD expulsion at 1 year and 5 years, stratified by menorrhagia status; pooled and by research site, first observed IUD insertions

Research site and menor-rhagia in the past year	No. of inser-tions	Person-years	No. of events	Crude incidence rate (95% CI)	Crude cumulative incidence, 1 year (95 CI), %	Crude cumulative incidence, 5 years (95 CI), %
Complete study population						
Pooled						
Yes	32,552	64,034.5	2,533	39.56 (38.03, 41.13)	6.89 (6.60, 7.20)	11.89 (11.40, 12.41)
No	294,106	577,392.7	6,410	11.10 (10.83, 11.38)	1.78 (1.73, 1.84)	3.72 (3.61, 3.83)
KPNC						
Yes	13,593	27,023.3	1,219	45.11 (42.61, 47.71)	7.58 (7.10, 8.09)	14.13 (13.30, 15.00)
No	147,849	298,528.2	3,816	12.78 (12.38, 13.19)	2.01 (1.94, 2.09)	4.45 (4.28, 4.62)
KPSC						
Yes	15,727	30,649.3	1,181	38.53 (36.37, 40.79)	7.02 (6.60, 7.47)	10.82 (10.17, 11.51)
No	107,487	211,273.9	1,991	9.42 (9.01, 9.85)	1.62 (1.53, 1.70)	2.93 (2.78, 3.09)
KPWA						
Yes	2,027	3,898.6	86	22.06 (17.64, 27.24)	3.21 (2.46, 4.20)	8.01 (6.27, 10.21)
No	18,499	33,597.6	350	10.42 (9.35, 11.57)	1.58 (1.39, 1.80)	3.65 (3.20, 4.16)
RI						
Yes	1,205	2,463.3	47	19.08 (14.02, 25.37)	3.40 (2.44, 4.75)	6.09 (4.40, 8.40)
No	20,271	33,993.0	253	7.44 (6.55, 8.42)	1.13 (0.98, 1.30)	2.17 (1.82, 2.59)
Study population more than 52 weeks postpartum or with no recorded delivery						
Pooled						
Yes	31,600	62,405.4	2,497	40.01 (38.46, 41.61)	7.00 (6.70, 7.32)	12.03 (11.52, 12.55)
No	197,234	390,598.3	4,265	10.92 (10.59, 11.25)	1.77 (1.71, 1.84)	3.69 (3.56, 3.83)
KPNC						
Yes	13,204	26,366.7	1,201	45.55 (43.01, 48.20)	7.68 (7.19, 8.20)	14.27 (13.43, 15.15)
No	102,307	210,809.5	2,604	12.35 (11.88, 12.84)	1.96 (1.87, 2.06)	4.35 (4.16, 4.56)
KPSC						
Yes	15,297	29,916.5	1,166	38.98 (36.77, 41.28)	7.14 (6.70, 7.60)	10.94 (10.28, 11.63)
No	66,848	132,799.2	1,252	9.43 (8.91, 9.96)	1.66 (1.56, 1.77)	2.95 (2.76, 3.15)

Research site and menor-rhagia in the past year	No. of inser-tions	Person-years	No. of events	Crude incidence rate (95% CI)	Crude cumulative incidence, 1 year (95 CI), %	Crude cumulative incidence, 5 years (95 CI), %
KPWA						
Yes	1,961	3,779.1	84	22.23 (17.73, 27.52)	3.26 (2.49, 4.26)	8.08 (6.31, 10.33)
No	12,740	23,470.8	243	10.35 (9.09, 11.74)	1.58 (1.36, 1.84)	3.61 (3.09, 4.21)
RI						
Yes	1,138	2,343.0	46	19.63 (14.37, 26.19)	3.50 (2.49, 4.90)	6.31 (4.55, 8.72)
No	15,339	23,518.9	166	7.06 (6.03, 8.22)	1.06 (0.90, 1.26)	1.88 (1.50, 2.36)

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

Source: Analysis Tables 8.1 through 8.5 and Additional Analysis Table 8.13.

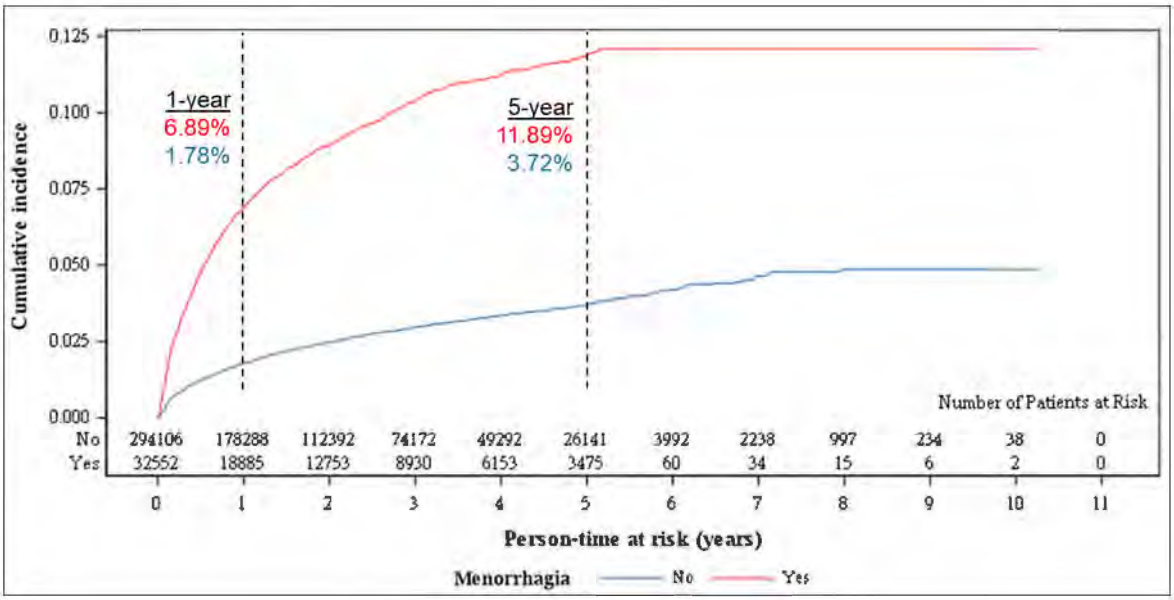


Figure 34: Crude cumulative incidence of IUD expulsion by menorrhagia status for the pooled complete study population (source: data from Analysis Table 8.1, Analysis Figure 12.1)

IUD = intrauterine device.

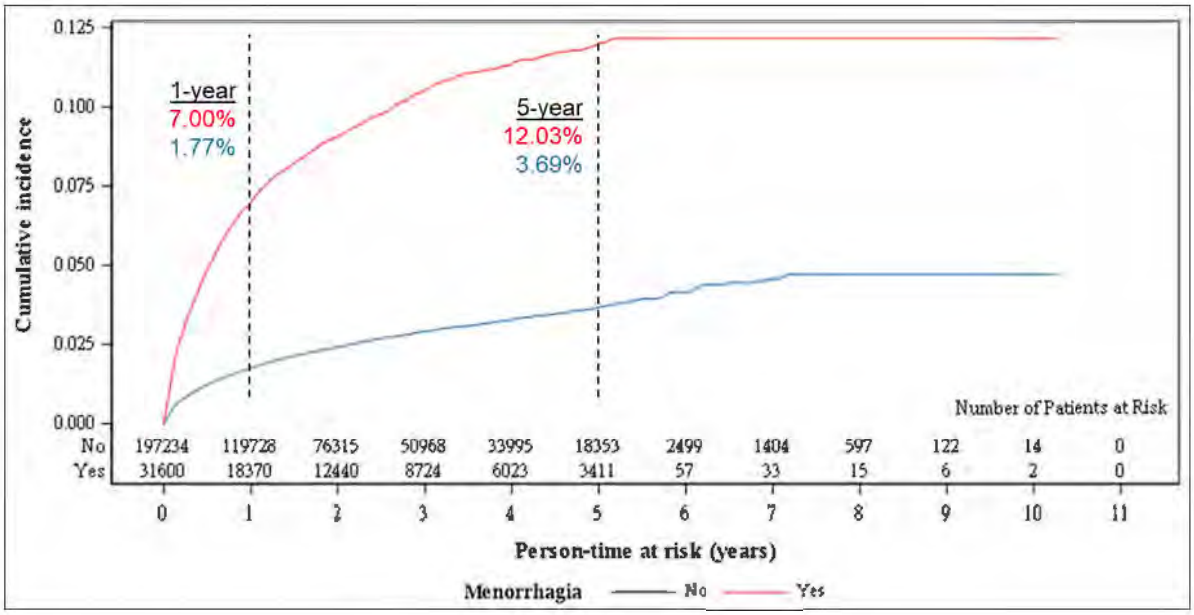


Figure 35: Crude cumulative incidence of IUD expulsion by menorrhagia status for the pooled study population excluding women with a delivery in the previous 52 weeks (source: data from Additional Analysis Table 8.13, Additional Analysis Figure 12.2.1)

IUD = intrauterine device.

For the complete study population and the study population with no delivery in the previous 52 weeks, the crude incidence rates and cumulative incidence at 1 and 5 years for IUD expulsion were higher among those with menorrhagia for the pooled data and for each research site. The crude incidence rates for the pooled complete study population were 39.56 per 1,000 person-years for those with a recent diagnosis of menorrhagia and 11.10 per 1,000 person-years for those without a recent diagnosis. In the pooled study population without a delivery in the previous 52 weeks, the crude incidence rates were 40.01 per 1,000 person-years for those with a recent diagnosis of menorrhagia and 10.92 per 1,000 person-years for those without a recent diagnosis.

10.5.9.2 IUD expulsion and menorrhagia, risk—first observed IUD insertions (objective 27: complete study population [per protocol] and excluding those with a delivery in the previous 52 weeks [additional analysis])

Objective 27: To estimate the adjusted hazard ratio of IUD expulsion for women using an IUD who have at least one diagnosis code indicating menorrhagia in the 12 months before IUD insertion versus IUD users who do not have this indication (this analysis will be performed only if there are more than 20,000 IUD users with an indication of menorrhagia that can be included in the analysis)

The crude and propensity score–adjusted HRs IUD expulsion and for menorrhagia, for first IUD insertions for the complete study population, are shown in Figure 36 (pooled). These same results for the study population excluding women with a delivery in the previous 52 weeks are shown in Figure 37 (pooled).

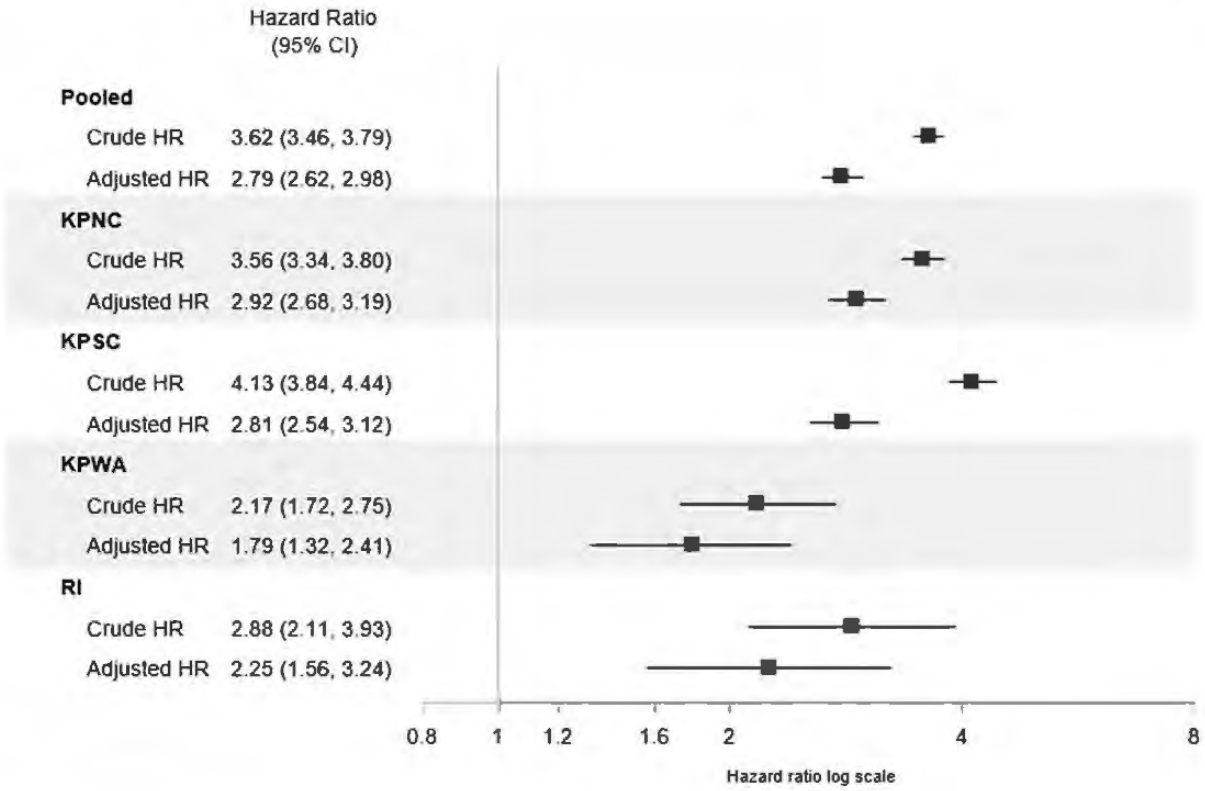


Figure 36: Crude and propensity score–adjusted hazard ratios for IUD expulsion for women with a history of menorrhagia at IUD insertion compared with women who did not have a history of menorrhagia; pooled and by site, complete study population, first observed IUD insertions (source: data from Analysis Table 27.1, pooled and by research site)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute.

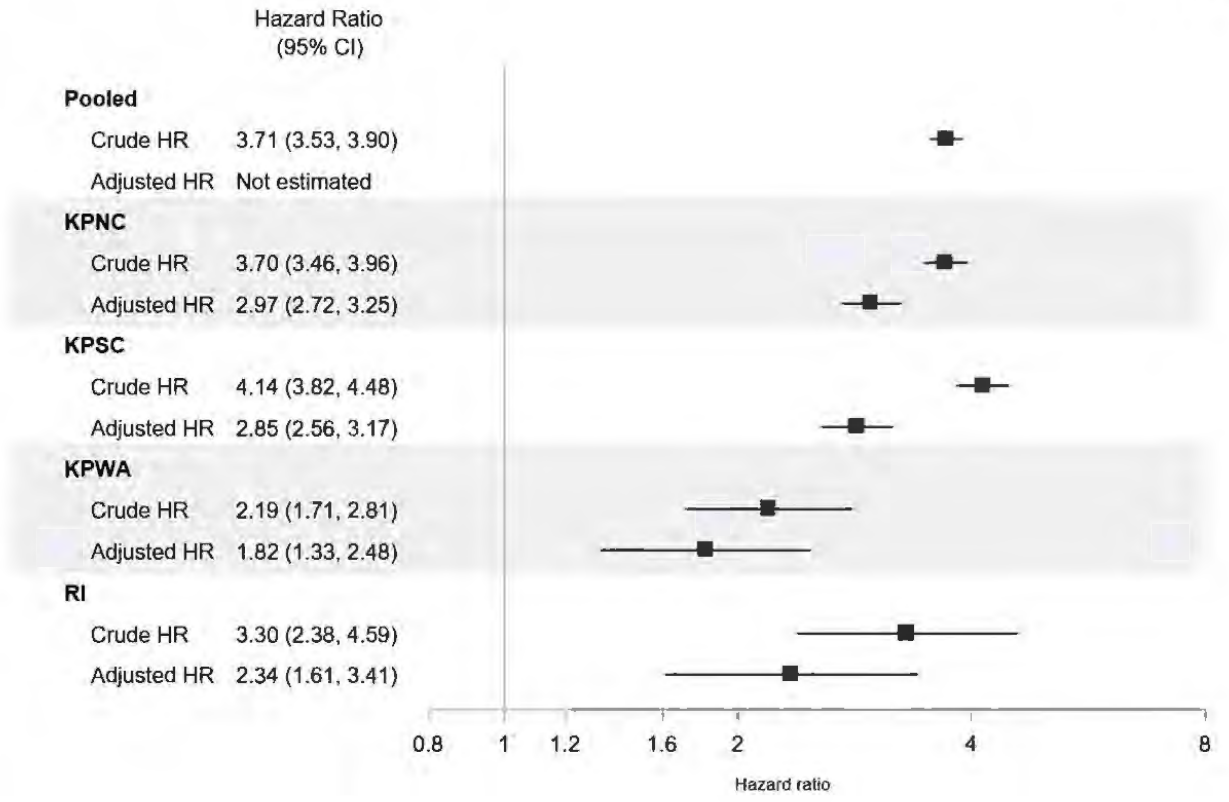


Figure 37: Crude and propensity score–adjusted hazard ratios for IUD expulsion for women with a history of menorrhagia at IUD insertion compared with women who did not have a history of menorrhagia; pooled and by site, study population excluding those with a delivery in the previous 52 weeks, first observed IUD insertions (source: data from Additional Analysis Table 27.4, pooled and by research site)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute.

In crude analyses, for both the complete study population and for the study population excluding those with a delivery in the previous 52 weeks, women with menorrhagia in the past year were more likely to have IUD expulsion than women who did not have menorrhagia in the past year (pooled complete study population, crude HR, 3.62; pooled study population without a delivery in the previous 52 weeks, crude HR, 3.71). The proportional hazards assumption was satisfied through 5 years after insertion. Standardized differences prior to confounding adjustment were substantial (absolute standardized difference for any level of a variable > 0.2) between women with and without menorrhagia (pooled: Analysis Table 19.2.1; by site: Analysis Tables 19.2.2-19.2.5). After propensity score weighting using initial propensity score models, all levels of all variables had satisfactory balance (absolute standardized difference < 0.2), overall and at all sites, except age, dysmenorrhea, concomitant gynecological procedure, and any difficult insertion at RI (Analysis Tables 27.3.1-27.3.5 and Analysis Figures 27.1.1-27.1.5). An interaction term between site and age tertiles was added, and age had satisfactory balance. At RI, dysmenorrhea, concomitant gynecological procedure and any difficult insertion remained less well balanced (absolute standardized difference, 0.2-0.3).

In the pooled analysis and across all research sites, after adjustment, women with menorrhagia in the past year remained more likely to have a diagnosis of IUD expulsion than women who did not have menorrhagia in the past year, although this was attenuated after confounding adjustment in both the complete study population and among those without a delivery in the previous 52 weeks. There was a statistical interaction between the menorrhagia status and research site. These HRs are consistent with the trends in crude incidence and cumulative incidence.

10.5.10 Uterine perforation and postpartum timing, breastfeeding, and IUD type interactions—first observed IUD insertions (objectives 28, 29, 31)

10.5.10.1 Uterine perforation and interaction of breastfeeding with postpartum timing—first observed IUD insertions (objective 28)

Objective 28: To evaluate the extent to which breastfeeding status (yes vs. no) modified the association of uterine perforation for women with IUD insertion at different time periods postpartum (i.e., IUD insertion ≤ 14 weeks versus IUD insertion > 14 weeks postpartum) among women with a recorded delivery within the past 52 weeks at the time of the first observed IUD insertion

The crude incidence rate (per 1,000 person-years) and the 1-year and 5-year cumulative incidence rates of uterine perforation stratified by breastfeeding status (yes vs. no) and postpartum timing at the time of IUD insertion (≤ 14 vs. > 14 weeks postpartum) for first IUD insertion are shown in Table 37. The crude and propensity score–adjusted HRs for uterine perforation for assessment of the statistical interaction between breastfeeding status at IUD insertion (yes vs. no) and postpartum timing of IUD insertion (≤ 14 weeks vs. > 14 weeks), first IUD insertions, are shown in Table 38.

Table 37: Crude incidence rate (per 1,000 person-years) and cumulative incidence of uterine perforation at 1 year and 5 years, stratified by breastfeeding status (yes vs. no) and postpartum timing at IUD insertion (≤ 14 weeks vs. > 14 to ≤ 52 weeks); pooled across research sites, first observed IUD insertions, study population with breastfeeding status available

Exposure group	Insertions	Person-years	Events	Crude incidence rate (95% CI)	1-year crude cumulative incidence (95 CI), %	5-year crude cumulative incidence (95 CI), %
Breastfeeding, ≤ 14 weeks	55,553	107,726.5	471	4.37 (3.99, 4.79)	0.61 (0.55, 0.69)	1.69 (1.49, 1.91)
Breastfeeding, > 1 4 to ≤ 52 weeks	8,633	16,176.3	55	3.40 (2.56, 4.43)	0.50 (0.36, 0.69)	1.08 (0.78, 1.50)
Not breastfeeding, ≤ 14 weeks	18,724	36,625.6	121	3.30 (2.74, 3.95)	0.47 (0.37, 0.59)	1.16 (0.93, 1.45)
Not breastfeeding, > 14 to ≤ 52 weeks	11,907	22,210.0	26	1.17 (0.76, 1.72)	0.17 (0.11, 0.28)	0.41 (0.24, 0.69)

CI = confidence interval; IUD = intrauterine device.
Source: Additional Analysis Table 3.9.

The crude incidence rates and 1-year and 5-year cumulative incidence of uterine perforation were higher in the earlier postpartum IUD insertion group (≤ 14 weeks) than in the later postpartum group (> 14 to ≤ 52 weeks), within each breastfeeding strata. Also, the crude incidence rate and 1-year and 5-year cumulative incidence of uterine perforation in women who were breastfeeding at the time of IUD insertion were higher than in those who were not breastfeeding within the same postpartum timing strata. Incidence of uterine perforation was highest in those with IUD insertions ≤ 14 weeks

postpartum who were breastfeeding. Incidence of uterine perforation was lowest in those with IUD insertions > 14 to ≤ 52 weeks postpartum who were not breastfeeding at the time of IUD insertion.

Table 38: Crude and propensity score–adjusted hazard ratios for uterine perforation for assessment of effect modification of breastfeeding status at the time of IUD insertion (yes vs. no) on postpartum timing of IUD insertion (≤ 14 weeks vs. > 14 to ≤ 52 weeks postpartum); pooled across research sites, first observed IUD insertions, study population with breastfeeding status available

Statistic	Postpartum status	Breastfeeding status		HR (95% CI) (breastfeeding yes vs. no)
		Yes	No	
Crude HR (95% CI)	≤ 14 weeks	3.77 (2.54, 5.60)	2.89 (1.89, 4.41)	**1.31 (1.07, 1.60)**
	> 14 to ≤ 52 weeks	2.90 (1.82, 4.62)	1.00 (Reference)	**2.90 (1.82, 4.62)**
	HR (95% CI) ≤ 14 weeks vs. > 14 to ≤ 52 weeks	**1.30 (0.98, 1.72)**	**2.89 (1.89, 4.41)**	
Propensity score–adjusted HR (95% CI)	≤ 14 weeks	3.28 (2.17, 4.97)	2.56 (1.62, 4.02)	**1.28 (1.02, 1.61)**
	> 14 to ≤ 52 weeks	2.41 (1.47, 3.95)	1.00 (Reference)	**2.41 (1.47, 3.95)**
	HR (95% CI) ≤ 14 weeks vs. > 14 to ≤ 52 weeks	**1.36 (1.01, 1.83)**	**2.56 (1.62, 4.02)**	

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.
Note: *P* = 0.0229 type 3 group test for statistical interaction of breastfeeding status and postpartum status.
Source: Analysis Table 28.1.

The study population of women ≤ 52 weeks postpartum with breastfeeding status available was included in this analysis. The proportional hazards assumption was satisfied as determined by visual inspection of the curves. Standardized differences prior to confounding adjustment were modest (Analysis Table 28.2.1 and Analysis Figure 28.1.1). After propensity score weighting, all of the variables included in the model had satisfactory balance (absolute standardized difference < 0.2) (Analysis Table 28.3.1 and Analysis Figure 28.1.1).

For the propensity score–adjusted analysis, among those who were not breastfeeding at the time of IUD insertion, risk of uterine perforation with early postpartum IUD insertion (≤ 14 weeks) was 2.6 times the risk for those with later postpartum insertion (> 14 to ≤ 52 weeks postpartum) (adjusted HR, 2.56). Among those who were breastfeeding at the time of IUD insertion, there was a more modest 36% higher risk of perforation with early postpartum IUD insertion compared with later postpartum IUD insertion (adjusted HR, 1.36). Similarly, for those who were > 14 weeks postpartum at the time of the insertion, the risk was 2.4 times the risk of uterine perforation in those who were breastfeeding at the time of IUD insertion compared with those who were not (adjusted HR, 2.41). For those who were ≤ 14 weeks postpartum at the time of IUD insertion, the risk of uterine perforation was about 30% higher for those who were breastfeeding at the time of IUD insertion than for those who were not (adjusted HR, 1.28). Thus, for risk of uterine perforation, a statistically significant departure from a multiplicative relation was seen between breastfeeding status and postpartum timing of IUD insertion (*P* = 0.023 for the interaction term).

Despite the interaction effect between breastfeeding status and postpartum timing of IUD insertion, risk of uterine perforation was highest in those with IUD insertions ≤ 14 weeks postpartum who were breastfeeding (adjusted HR, 3.28), followed by those with IUD insertions ≤ 14 weeks postpartum who were not breastfeeding (adjusted HR, 2.56), and those with IUD insertions > 14 to

≤ 52 weeks postpartum who were breastfeeding (adjusted HR, 2.41) all compared with those with IUD insertions > 14 to ≤ 52 weeks postpartum who were not breastfeeding.

10.5.10.2 Uterine perforation with interaction of IUD type with breastfeeding—first observed IUD insertions (objective 29)

Objective 29: To evaluate the extent to which type of IUD (LNG-IUD vs. copper IUD) modified the association between uterine perforation and breastfeeding among women who were and were not breastfeeding at the time of first observed IUD insertion

The crude incidence rate (per 1,000 person-years) and the 1-year and 5-year cumulative incidence rates of uterine perforation stratified by IUD type (LNG vs. copper) and breastfeeding status (yes vs. no) at the time of IUD insertion for first IUD insertions are shown in Table 39. The crude and propensity score–adjusted HRs for uterine perforation for assessment of the effect modification of IUD type on breastfeeding status at IUD insertion, first IUD insertions, are shown in Table 40.

Table 39: Crude incidence rate (per 1,000 person-years) and cumulative incidence of uterine perforation at 1 year and 5 years, stratified by IUD type and breastfeeding status at the time of IUD insertion; pooled across research sites, first observed IUD insertions, study population with breastfeeding status available

Exposure group	Insertions	Person-years	Events	Crude incidence rate (95% CI)	1-year crude cumulative incidence (95 CI), %	5-year crude cumulative incidence (95 CI), %
LNG-IUD, breastfeeding	48,447	91,918.4	439	4.78 (4.34, 5.24)	0.65 (0.58, 0.73)	1.79 (1.57, 2.03)
LNG-IUD, not breastfeeding	23,754	44,758.2	130	2.90 (2.43, 3.45)	0.40 (0.32, 0.50)	1.05 (0.84, 1.30)
Copper IUD, breastfeeding	15,330	31,299.9	83	2.65 (2.11, 3.29)	0.41 (0.32, 0.54)	1.09 (0.81, 1.46)
Copper IUD, not breastfeeding	6,674	13,677.8	16	1.17 (0.67, 1.90)	0.20 (0.11, 0.35)	0.26 (0.15, 0.45)

CI = confidence interval; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.
Source: Additional Analysis Table 3.9.

For each type of IUD, the crude incidence rates and 1-year and 5-year cumulative incidence of uterine perforation were higher in women who were breastfeeding at IUD insertion than in those not breastfeeding. Also, the crude incidence rates and 1-year and 5-year cumulative incidence of uterine perforation in those receiving an LNG-IUD were higher than in those receiving a copper IUD within each breastfeeding stratum.

Table 40: Crude and adjusted hazard ratios for uterine perforation for assessment of effect modification of IUD type on breastfeeding status at the time of IUD insertion; pooled across research sites, first observed IUD insertions, study population with breastfeeding status available

Exposure group	Number of events	Number of insertions	Crude HR (95% CI)	Propensity score–adjusted HR (95% CI)
LNG-IUD, breastfeeding	439	48,447	1.64 (1.35, 1.99)	1.33 (1.07, 1.64)
LNG-IUD, not breastfeeding	130	23,754	1.00 (Reference)	1.00 (Reference)
Copper IUD, breastfeeding	83	15,330	2.28 (1.33, 3.89)	1.66 (0.94, 2.94)
Copper IUD, not breastfeeding	16	6,674	1.00 (Reference)	1.00 (Reference)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.
P = 0.4669 type 3 group test for statistical interaction with breastfeeding status.
Source: Additional Analysis Table 29.1.

The study population with breastfeeding status available was included for this analysis, i.e., those ≤ 52 weeks postpartum. The proportional hazards assumption was satisfied as determined by visual inspection of the curves. Propensity score weighting was conducted using the weights developed for the breastfeeding status–uterine perforation model (objective 1).

For the propensity score–adjusted analysis, among those who received an LNG-IUD, there was a 33% higher risk of uterine perforation in women who were breastfeeding at the time of IUD insertion (adjusted HR, 1.33) than in those who were not breastfeeding. For those who received a copper IUD, the propensity score–adjusted risk of uterine perforation was 66% higher in women who were breastfeeding at the time of IUD insertion than in those who were not breastfeeding (adjusted HR, 1.66). The statistical interaction between IUD type and breastfeeding status was not significant for uterine perforation (*P* = 0.47).

10.5.10.3 Uterine perforation with IUD type x postpartum timing–first observed IUD insertions (objective 31)

Objective 31: To evaluate the extent to which type of IUD (LNG-IUD vs. copper IUD) modified the association between uterine perforation and postpartum timing of IUD insertion for women with IUD insertion at different time periods postpartum (i.e., ≤ 6 weeks, > 6 and ≤ 14 weeks, > 14 and ≤ 52 weeks) versus IUD insertion more than 52 weeks postpartum, including no recorded delivery within the past 52 weeks, at the time of the first observed IUD insertion

The crude incidence rate (per 1,000 person-years) and the 1-year and 5-year cumulative incidence rates of uterine perforation stratified by IUD type (LNG vs. copper) and postpartum timing of IUD insertion (≤ 6 weeks, > 6 to ≤ 14 weeks, > 14 to ≤ 52 weeks and > 52 weeks or no recorded delivery), for first IUD insertion, are shown in Table 41. The crude, propensity score–adjusted, and fully adjusted HRs for four-category postpartum status and uterine perforation, stratified by IUD type, are shown in Table 42.

Table 41: Crude incidence rate (per 1,000 person-years) and cumulative incidence of uterine perforation at 1 year and 5 years, stratified by IUD type and postpartum timing of IUD insertion (4 categories); pooled across research sites, first observed IUD insertions, complete study population

Exposure group	Insertions	Person-years	Events	Crude incidence rate (95% CI)	1-year crude cumulative incidence (95 CI), %	5-year crude cumulative incidence (95 CI), %
LNG-IUD, ≤ 6 weeks	15,631	28,317.9	160	5.65 (4.81, 6.60)	0.78 (0.64, 0.94)	2.10 (1.68, 2.64)
LNG-IUD, > 6 to ≤ 14 weeks	42,760	83,032.8	358	4.31 (3.88, 4.78)	0.59 (0.52, 0.68)	1.60 (1.40, 1.83)
LNG-IUD, > 14 to ≤ 52 weeks	16,110	29,479.3	73	2.48 (1.94, 3.11)	0.34 (0.26, 0.46)	0.83 (0.62, 1.11)
LNG-IUD, > 52 weeks or no delivery	184,733	366,321.2	243	0.66 (0.58, 0.75)	0.07 (0.06, 0.09)	0.28 (0.24, 0.32)
Copper IUD, ≤ 6 weeks	4,228	8,471.7	30	3.54 (2.39, 5.06)	0.47 (0.29, 0.77)	1.25 (0.77, 2.03)
Copper IUD, > 6 to ≤ 14 weeks	12,934	26,936.7	54	2.00 (1.51, 2.62)	0.33 (0.24, 0.46)	0.81 (0.56, 1.16)
Copper IUD, > 14 to ≤ 52 weeks	5,379	10,744.0	17	1.58 (0.92, 2.53)	0.29 (0.16, 0.49)	0.51 (0.27, 0.97)
Copper IUD, > 52 weeks or no delivery	41,123	81,434.5	61	0.75 (0.57, 0.96)	0.06 (0.04, 0.09)	0.40 (0.29, 0.55)

CI = confidence interval; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.
Source: Additional Analysis Table 3.9.

For each type of IUD, the crude incidence rates and 1-year and 5-year cumulative incidence of uterine perforation were higher in the earlier postpartum group and decreased with later postpartum time of IUD insertion. Also, within each postpartum timing stratum, the crude incidence rates and 1-year and 5-year cumulative incidence of uterine perforation in those receiving an LNG-IUD were higher than in those receiving a copper IUD, with one exception. Within the > 52 week/no delivery group, the incidence was comparable between the two IUD types or slightly higher in the copper IUD group.

Table 42: Crude and adjusted hazard ratios for uterine perforation for assessment of effect modification of IUD type on postpartum timing of IUD insertion (4-level); pooled across research sites, first observed IUD insertions, complete study population

Exposure group	Number of events	Number of insertions	Crude HR (95% CI)	Propensity score–adjusted HR (95% CI)	Fully adjusted HR[a] (95% CI)
LNG-IUD, ≤ 6 weeks	160	15,631	8.35 (6.84, 10.20)	9.21 (7.06, 12.03)	6.78 (4.74, 9.70)
LNG-IUD, > 6 to ≤ 14 weeks	358	42,760	6.51 (5.53, 7.66)	6.75 (5.32, 8.55)	5.11 (3.75, 6.95)
LNG-IUD, > 14 to ≤ 52 weeks	73	16,110	3.67 (2.83, 4.77)	3.80 (2.75, 5.26)	3.13 (2.21, 4.42)
LNG-IUD, > 52 weeks or no delivery	243	184,733	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Copper IUD, ≤ 6 weeks	30	4,228	4.73 (3.06, 7.33)	5.83 (3.40, 9.98)	4.30 (2.38, 7.75)
Copper IUD, > 6 to ≤ 14 weeks	54	12,934	2.69 (1.87, 3.88)	3.49 (2.17, 5.61)	2.61 (1.56, 4.36)
Copper IUD, > 14 to ≤ 52 weeks	17	5,379	2.09 (1.22, 3.58)	2.49 (1.31, 4.72)	2.01 (1.05, 3.85)
Copper IUD, > 52 weeks or no delivery	61	41,123	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.

Note: type 3 group test for statistical interaction with postpartum timing: $P = 0.1143$ (propensity score–adjusted HR) and $P = 0.1040$ (fully adjusted HR).

[a] Note: "Fully" adjusted = adjusted for propensity score and breastfeeding status.

Source: Analysis Table 31.1.

Propensity score weighting was conducted using the weights developed for the four-category postpartum status–uterine perforation model (objective 2).

In the crude and adjusted results, women with earlier postpartum insertions had a higher risk of uterine perforation than women in the referent group (> 52 weeks postpartum or no recorded delivery) and there was a trend for lower risk with increasing IUD insertion postpartum time for both types of IUD.

The type 3 group test for statistical interaction between IUD type and postpartum timing for the outcome of uterine perforation was not statistically significant after confounding adjustment via propensity scores ($P = 0.1143$) or after confounding adjustment including propensity score weighting and breastfeeding ($P = 0.1040$).

10.5.11 IUD expulsion and postpartum timing, breastfeeding, and IUD type interactions–first observed IUD insertions (objectives 30, 32)

10.5.11.1 IUD expulsion with IUD type x breastfeeding–first observed IUD insertions (objective 30)

Objective 30: To evaluate the extent to which type of IUD (LNG-IUD vs. copper IUD) modified the association between IUD expulsion and breastfeeding among women who were and were not breastfeeding at the time of first observed IUD insertion

The crude incidence rate (per 1,000 person-years) and the 1-year and 5-year cumulative incidence rates of IUD expulsion stratified by IUD type (LNG vs. copper) and breastfeeding status (yes vs. no) at the time of IUD insertion for first IUD insertion are shown in Table 43. The crude and propensity score–adjusted HRs for IUD expulsion for assessment of the effect modification of IUD type on breastfeeding status at IUD insertion, for first IUD insertion, are shown in Table 44.

Table 43: Crude incidence rate (per 1,000 person-years) and cumulative incidence of IUD expulsion at 1 year and 5 years, stratified by IUD type and breastfeeding status at the time of IUD insertion; pooled across research sites, first observed IUD insertions, study population with breastfeeding status available

Exposure group	Insertions	Person-years	Events	Crude incidence rate (95% CI)	1-year crude cumulative incidence (95 CI), %	5-year crude cumulative incidence (95 CI), %
LNG-IUD, breastfeeding	48,447	91,918.4	913	9.93 (9.30, 10.60)	1.46 (1.35, 1.58)	3.42 (3.15, 3.71)
LNG-IUD, not breastfeeding	23,754	44,758.2	643	14.37 (13.28, 15.52)	2.36 (2.16, 2.59)	4.52 (4.11, 4.97)
Copper IUD, breastfeeding	15,330	31,299.9	343	10.96 (9.83, 12.18)	1.79 (1.58, 2.04)	3.66 (3.24, 4.15)
Copper IUD, not breastfeeding	6,674	13,677.8	211	15.43 (13.42, 17.65)	2.80 (2.39, 3.27)	4.88 (4.17, 5.69)

CI = confidence interval; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.
Source: Additional Analysis Table 8.9.

For each type of IUD, the crude incidence rates and 1-year and 5-year cumulative incidence of IUD expulsion were lower in women who were breastfeeding at IUD insertion than in those not breastfeeding. Within each breastfeeding stratum, the crude incidence rates and 1-year and 5-year cumulative incidence of IUD expulsion in those receiving an LNG-IUD were modestly lower than in those receiving a copper IUD.

Table 44: Crude and propensity score–adjusted hazard ratios for IUD expulsion for assessment of effect modification of IUD type on breastfeeding status at the time of IUD insertion; pooled across research sites, first observed IUD insertions study population with breastfeeding status available

Exposure group	Number of events	Number of insertions	Crude HR (95% CI)	Propensity score–adjusted HR (95% CI)
LNG-IUD, breastfeeding	913	48,447	0.68 (0.62, 0.76)	0.72 (0.64, 0.80)
LNG-IUD, not breastfeeding	643	23,754	1.00 (Reference)	1.00 (Reference)
Copper IUD, breastfeeding	343	15,330	0.69 (0.58, 0.82)	0.66 (0.54, 0.80)
Copper IUD, not breastfeeding	211	6,674	1.00 (Reference)	1.00 (Reference)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.
Note: type 3 group test for statistical interaction with breastfeeding status, *P* = 0.4366.
Source: Analysis Table 30.1.

The study population with breastfeeding status available was included for this analysis. The proportional hazards assumption was satisfied as determined by visual inspection of the curves. Propensity score weighting was conducted using the weights developed for the breastfeeding status–IUD expulsion model (objective 20).

For the propensity score–adjusted analysis, there was 28% lower risk of IUD expulsion for women who received an LNG-IUD and were breastfeeding at the time of IUD insertion than for those who were not breastfeeding (adjusted HR, 0.72). The propensity score–adjusted risk of IUD expulsion was 34% lower for women who received a copper IUD and were breastfeeding at the time of IUD insertion than for those who were not breastfeeding (adjusted HR, 0.66). The statistical interaction between IUD type and breastfeeding status was not significant (*P* = 0.44) for IUD expulsion.

10.5.11.2 IUD expulsion with IUD type x postpartum timing–first observed IUD insertions (objective 32)

Objective 32: To evaluate the extent to which type of IUD (LNG-IUD vs. copper IUD) modified the association between IUD expulsion and postpartum timing of IUD insertion for women with IUD insertion at different time periods postpartum (i.e., ≤ 6 weeks, > 6 and ≤ 14 weeks, > 14 and ≤ 52 weeks) versus IUD insertion more than 52 weeks postpartum, including no recorded delivery within the past 52 weeks, at the time of the first observed IUD insertion

The crude incidence rate (per 1,000 person-years) and the 1-year and 5-year cumulative incidence rates of IUD expulsion stratified by IUD type (LNG vs. copper) and postpartum timing of IUD insertion (≤ 6 weeks, > 6 to ≤ 14 weeks, > 14 to ≤ 52 weeks, and > 52 weeks or no recorded delivery) for first IUD insertions are shown in Table 45. The pooled crude, propensity score–adjusted, and fully adjusted HRs for IUD expulsion with four-category postpartum status, stratified by IUD type, are shown in Table 46.

Table 45. Crude incidence rate (per 1,000 person-years) and cumulative incidence of IUD expulsion at 1 year and 5 years, stratified by IUD type and postpartum timing of IUD insertion; pooled across research sites, first observed IUD insertions, complete study population

Exposure group	Insertions	Person-years	Events	Crude incidence rate (95% CI)	1-year crude cumulative incidence (95 CI), %	5-year crude cumulative incidence (95 CI), %
LNG-IUD, ≤ 6 weeks	15,631	28,317.9	440	15.54 (14.12, 17.06)	2.46 (2.21, 2.74)	4.83 (4.28, 5.45)
LNG-IUD, > 6 to ≤ 14 weeks	42,760	83,032.8	747	9.00 (8.36, 9.67)	1.30 (1.19, 1.43)	3.13 (2.86, 3.42)
LNG-IUD, > 14 to ≤ 52 weeks	16,110	29,479.3	407	13.81 (12.50, 15.22)	2.20 (1.96, 2.46)	4.42 (3.92, 4.99)
LNG-IUD, > 52 weeks or no delivery	184,733	366,321.2	5,481	14.96 (14.57, 15.36)	2.52 (2.45, 2.60)	4.82 (4.67, 4.98)
Copper IUD, ≤ 6 weeks	4,228	8,471.7	124	14.64 (12.17, 17.45)	2.44 (1.97, 3.02)	4.86 (3.93, 6.00)
Copper IUD, > 6 to ≤ 14 weeks	12,934	26,936.7	273	10.13 (8.97, 11.41)	1.72 (1.49, 1.99)	3.36 (2.92, 3.86)
Copper IUD, > 14 to ≤ 52 weeks	5,379	10,744.0	171	15.92 (13.62, 18.49)	2.72 (2.28, 3.24)	4.94 (4.17, 5.86)
Copper IUD, > 52 weeks or no delivery	41,123	81,434.5	1,229	15.09 (14.26, 15.96)	2.42 (2.26, 2.59)	5.27 (4.92, 5.64)

CI = confidence interval; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.
Source: Additional Analysis Table 8.9.

For women with an LNG-IUD, the crude incidence rates and 1-year and 5-year cumulative incidence of IUD expulsion were highest in the group with IUD insertion ≤ 6 weeks postpartum, lowest in the group with IUD insertion > 6 to ≤ 14 weeks postpartum, and intermediate in the other two groups defined by postpartum timing of IUD insertion. Among those receiving a copper IUD, the pattern was the same in the two earliest postpartum timing groups, but the crude incidence and 1-year cumulative incidence were slightly higher for IUD insertion > 14 to ≤ 52 weeks postpartum than for IUD insertion > 52 weeks or no delivery within the previous year. In the earliest IUD insertion group (≤ 6 weeks postpartum), the crude incidence rate of IUD expulsion and the 1-year and 5-year cumulative incidence are not appreciably different for the two IUD types. In the three later postpartum timing strata, the crude incidence rate and 1-year and 5-year cumulative incidence of IUD expulsion were slightly lower for women with LNG-IUDs than for those receiving a copper IUD with a single exception—the 1-year cumulative incidence estimate for IUD insertion > 52 weeks postpartum or with no delivery was slightly higher for LNG-IUDs than for the copper IUDs.

Table 46: Crude and adjusted hazard ratios for IUD expulsion for assessment of effect modification of IUD type on postpartum timing of IUD insertion (4 levels); pooled across research sites, first observed IUD insertions, complete study population

Exposure group	Number of events	Number of insertions	Crude HR (95% CI)	Propensity score–adjusted HR (95% CI)	Fully adjusted HR[a] (95% CI)	HR, ≤ 49 days after IUD insertion (95% CI)	HR, > 49 days after IUD insertion (95% CI)
LNG-IUD, ≤ 6 weeks	440	15,631	0.99 (0.90, 1.09)	1.22 (1.09, 1.36)	1.59 (1.38, 1.82)	2.07 (1.70, 2.53)	1.42 (1.22, 1.66)
LNG-IUD, > 6 to ≤ 14 weeks	747	42,760	0.59 (0.55, 0.64)	0.80 (0.73, 0.88)	1.01 (0.90, 1.14)	0.90 0.75, 1.08)	1.05 (0.93, 1.19)
LNG-IUD, > 14 to ≤ 52 weeks	407	16,110	0.89 (0.80, 0.98)	1.21 (1.07, 1.36)	1.40 (1.23, 1.58)	1.40 (1.14, 1.72)	1.40 (1.22, 1.60)
LNG-IUD, > 52 weeks or no delivery	5,481	184,733	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Copper IUD, ≤ 6 weeks	124	4,228	0.97 (0.81, 1.17)	0.94 (0.77, 1.15)	1.23 (0.98, 1.53)	1.61 (1.22, 2.11)	1.11 (0.88, 1.39)
Copper IUD, > 6 to ≤ 14 weeks	273	12,934	0.68 (0.60, 0.78)	0.75 (0.65, 0.87)	0.96 (0.81, 1.13)	0.85 (0.68, 1.06)	1.00 (0.84, 1.18)
Copper IUD, > 14 to ≤ 52 weeks	171	5,379	1.06 (0.90, 1.24)	1.15 (0.97, 1.38)	1.35 (1.13, 1.63)	1.36 (1.06, 1.74)	1.36 (1.12, 1.64)
Copper IUD, > 52 weeks or no delivery	1,229	41,123	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.

Note: type 3 group test for statistical interaction of IUD type with postpartum timing of IUD insertion: *P* = 0.1918 (propensity score–adjusted HR) and *P* = 0.2009 (fully adjusted HR).

[a] "Fully" adjusted = adjusted for propensity score and breastfeeding status.

Source: Analysis Table 32.1.

Propensity score weighting was conducted using the weights developed for the four-category postpartum status–IUD expulsion model (objective 23). The proportional hazards assumption was not met for this analysis, and an inflection point in the log-log plot was identified at 49 days after IUD insertion. Thus, adjustment for a categorical interaction with time at 49 days after IUD insertion was also conducted (see results in Table 46).

In the crude and adjusted results, the same results were seen by IUD type as in the main analysis by four-category postpartum status. When compared with women with IUD insertion > 52 weeks postpartum or no delivery (referent), women with IUD insertion > 6 to ≤ 14 weeks postpartum had a lower or similar risk of IUD expulsion, while women with IUD insertion ≤ 6 weeks or > 14 to ≤ 52 weeks postpartum had a similar or higher risk.

The type 3 group test for statistical interaction between IUD type and postpartum timing for the outcome of IUD expulsion was not statistically significant after confounding adjustment via propensity scores ($P = 0.1918$), after confounding adjustment including propensity score weighting and breastfeeding status ($P = 0.2009$), or with the inclusion of the categorical interaction by time ($P = 0.2064$).

10.5.12 Subsequent insertion analyses for breastfeeding, postpartum timing, and IUD type with uterine perforation (objective 18)

Objective 18: To estimate the adjusted hazard ratios of uterine perforation described in objectives 1, 2, and 14 to *16 across all subsequent insertions (i.e., not the first insertion) observed within the data. (The site-specific analyses were performed only if there were more than 20,000 subsequent IUD insertions for that site. The pooled analysis included all sites regardless of the number of subsequent IUD insertions at a site.)*

The crude incidence rates and cumulative incidence of uterine perforation for all analyses of subsequent insertions (breastfeeding, postpartum timing, and IUD type) are in Additional Analysis Tables 3.10 through 3.12 provided in a stand-alone document (see list in Annex 1).

10.5.12.1 Breastfeeding and uterine perforation—subsequent insertions

The crude and propensity score–adjusted HRs for uterine perforation for subsequent IUD insertions, by breastfeeding status, are shown in Table 47. Only pooled analyses were conducted due to the occurrence of fewer than 20,000 insertions at all sites. The number of all subsequent IUD insertions in the 52 weeks after giving birth was 14,083.

Table 47: Crude and propensity score–adjusted hazard ratios for uterine perforation, by breastfeeding status; pooled across research sites, subsequent IUD insertions only

Breastfeeding status	No. of insertions	Person-years	No. of events	Crude HR (95% CI)	Propensity score–adjusted HR (95% CI)
Breastfeeding	9,772	16,659.2	77	1.80 (1.08, 3.01)	1.75 (0.99, 3.11)
Not breastfeeding	4,311	7,033.2	18	1.00 (Reference)	1.00 (Reference)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.
Source: Analysis Table 18.1.1.

The HR point estimates for the subsequent IUD insertions (crude HR, 1.80; adjusted HR, 1.75) are similar to the crude HR for initial insertions (HR, 1.69), although the point estimate for the analysis of subsequent insertions was not attenuated appreciably when adjusting for confounding, and the CIs are wider (due to fewer insertions).

10.5.12.2 Postpartum timing and uterine perforation—subsequent insertions

10.5.12.2.1 Four-category postpartum timing

The crude, propensity score–adjusted and fully adjusted HRs for the four-category postpartum timing and uterine perforation for subsequent IUD insertions are shown in Table 48.

Table 48: Crude and adjusted hazard ratios for uterine perforation for three categories of postpartum timing at subsequent IUD insertions compared with those who were more than 52 weeks postpartum or with no recorded delivery; pooled, complete study population, subsequent IUD insertions only

Weeks postpartum	No. of insertions	Person-years	No. of events	Crude HR (95% CI)	Propensity score–adjusted HR (95% CI)	Fully adjusted HR[a] (95% CI)
≤ 6	3,298	5,098.9	21	4.82 (2.94, 7.91)	4.42 (2.31, 8.45)	2.32 (0.92, 5.87)
> 6 to ≤ 14	7,122	12,570.8	54	5.32 (3.70, 7.67)	5.42 (3.17, 9.28)	2.97 (1.33, 6.65)
> 14 to ≤ 52	3,976	6,612.9	21	3.91 (2.39, 6.42)	3.92 (2.01, 7.65)	2.74 (1.31, 5.76)
> 52 or no delivery	46,114	73,420.8	62	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California.

[a] Note: "Fully" adjusted = adjusted for propensity score and breastfeeding status.

Source: Analysis Table 18.2.1, pooled and by research site (KPNC and KPSC only).

The complete study population with subsequent IUD insertions was included in this analysis. The number of all subsequent IUD insertions was only 60,510, compared with 326,658 first IUD insertions. The proportional hazards assumption was determined to be met based on visual inspection of the log-log survival curves, hazard functions, and global correlation test based on Schoenfeld residuals using the unweighted pooled data. Standardized differences prior to confounding adjustment were substantial (Analysis Table 18.2.2.1 and Analysis Figure 18.2.1 [pooled]; Analysis Tables 18.2.2.2-18.2.2.3 and Analysis Figures 18.2.2-18.2.3 [KPNC and KPSC]). After propensity score weighting, all of the variables included in the model had satisfactory balance (absolute standardized difference < 0.2) (Analysis Tables 18.2.3.1-18.2.3.3 and Analysis Figures 18.2.1-18.2.3). Breastfeeding could not be included in the propensity score model because in the category > 52 weeks postpartum, no woman was categorized as breastfeeding at the time of IUD insertion; breastfeeding status was included as a covariate separate from the propensity score model.

The fully adjusted HR point estimates for postpartum time at IUD insertion are 2.32 (≤ 6 weeks), 2.97 (> 6 to ≤ 14 weeks), and 2.74 (> 14 to ≤ 52 weeks); all are lower for the subsequent IUD insertions than for the first IUD insertions, although still in the direction of higher risk of uterine perforation than the group with IUD insertion > 52 weeks postpartum (or with no delivery identified). However, no apparent pattern across the three earlier postpartum IUD insertion categories can be identified.

10.5.12.2.2 Postpartum cut point at 14 weeks

The crude, propensity score–adjusted and fully adjusted HRs for uterine perforation for subsequent IUD insertions, for IUD insertion ≤ 14 weeks postpartum versus > 14 weeks postpartum or with no recorded delivery, are shown in Table 49.

Table 49: Crude, propensity score–adjusted, and fully adjusted hazard ratios for uterine perforation for postpartum timing at subsequent IUD insertion ≤ 14 weeks compared with those who were more than 14 weeks postpartum or with no recorded delivery; pooled complete study population, all subsequent IUD insertions

Weeks postpartum	No. of insertions	Person-years	No. of events	Crude HR (95% CI)	Propensity score–adjusted HR (95% CI)	Fully adjusted HR[a] (95% CI)
≤ 14	10,420	17,669.7	75	4.20 (3.07, 5.74)	4.31 (2.90, 6.38)	2.80 (1.29, 6.08)
> 14 or no delivery	50,090	80,033.7	83	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

CI = confidence interval; HR = hazard ratio, IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California.
[a] Fully adjusted = adjusted for propensity scores and breastfeeding status.
Source: Analysis Table 18.14.1, pooled and by research site (KPNC and KPSC only).

The complete study population with subsequent IUD insertions was included in this analysis. The number of all subsequent IUD insertions was only 60,510, compared with 326,658 first IUD insertions. The proportional hazards assumption was determined to be met based on visual inspection of the of log-log survival curves, hazard functions, and global correlation test based on Schoenfeld residuals using the unweighted pooled data. Standardized differences prior to confounding adjustment were substantial (Analysis Table 18.14.2.1 and Analysis Figure 18.14.1 [pooled]; Analysis Tables 18.14.2.2-18.14.2.3 and Analysis Figures 18.14.2-18.14.3 [KPNC and KPSC]). After propensity score weighting, all of the variables included in the model had satisfactory balance (absolute standardized difference < 0.2) (Analysis Tables 18.14.3.1-18.14.3.3 and Analysis Figures 18.14.1-18.14.3). Breastfeeding could not be included in the propensity score model because in the > 52-week postpartum category, no woman was categorized as breastfeeding at the time of IUD insertion; breastfeeding status was included as a covariate separate from the propensity score model.

The HR point estimates pooled across sites were lower for subsequent IUD insertions (crude HR, 4.20; propensity score–adjusted HR, 4.31; fully adjusted HR, 2.80) than for first insertions (crude HR, 5.07; propensity score–adjusted HR, 4.83; fully adjusted HR, 3.44), although they are still in the direction of higher risk of uterine perforation among the earlier postpartum group (≤ 14 weeks) than in the group with IUD insertions > 14 weeks postpartum (or with no delivery identified).

10.5.12.2.3 Postpartum cut point at 36 weeks

The crude, propensity score–adjusted, and fully adjusted HRs uterine perforation for subsequent IUD insertions ≤ 36 weeks postpartum versus > 36 weeks postpartum or with no recorded delivery are shown in Table 50.

Table 50: Crude, propensity score–adjusted, and fully adjusted hazard ratios for uterine perforation for postpartum timing at subsequent IUD insertion ≤ 36 weeks compared with women who were more than 36 weeks postpartum or with no recorded delivery; pooled complete study population, all subsequent IUD insertions

Weeks postpartum	No. of insertions	Person-years	No. of events	Crude HR (95% CI)	Propensity score–adjusted HR (95% CI)	Fully adjusted HR[a] (95% CI)
≤ 36	13,160	22,270.1	92	4.87 (3.55, 6.68)	5.05 (3.26, 7.83)	3.48 (1.62, 7.47)
> 36 or no delivery	47,350	75,433.4	66	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

CI = confidence interval; HR = hazard ratio, IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California.
[a] Fully adjusted = adjusted for propensity scores and breastfeeding status.
Source: Analysis Table 18.15.1, pooled and by research site (KPNC and KPSC only).

The complete study population with subsequent IUD insertions was included in this analysis. The number of all subsequent IUD insertions was only 60,510, compared with 326,658 first IUD insertions. The proportional hazards assumption was determined to be met based on visual inspection of the of log-log survival curves, hazard functions, and global correlation test based on Schoenfeld residuals using the unweighted pooled data. Standardized differences prior to confounding adjustment were substantial (Analysis Table 18.15.2.1 and Analysis Figure 18.15.1 [pooled]; Analysis Tables 18.15.2.2-18.15.2.3 and Analysis Figures 18.15.2-18.15.3 [KPNC and KPSC]). After propensity score weighting, all of the variables included in the model had satisfactory balance (absolute standardized difference < 0.2) (Analysis Tables 18.15.3.1-18.15.3.3 and Analysis Figures 18.15.1-18.15.3). Breastfeeding was not included in the propensity score model, but breastfeeding status was included as a covariate separate from the propensity score model.

The HR point estimates pooled across sites (crude HR, 4.87; adjusted HR, 5.05; fully adjusted HR, 3.48) were lower for subsequent IUD insertions than for first insertions (crude HR, 5.42; adjusted HR 5.89; fully adjusted HR, 4.36), although they are still in the direction of higher risk of uterine perforation among the earlier postpartum group (≤ 36 weeks) compared with the group with IUD insertions > 36 weeks postpartum (or with no delivery identified).

10.5.12.3 IUD type and uterine perforation–subsequent insertions

The crude and propensity score–adjusted HRs for LNG type and uterine perforation for subsequent IUD insertions, pooled across research sites, are shown in Table 51.

Table 51: Crude and propensity score–adjusted hazard ratios for uterine perforation for LNG-IUDs compared with copper IUDs; pooled across research sites, all subsequent IUD insertions

Weeks postpartum	No. of insertions	Person-years	No. of events	Crude HR (95% CI)	Propensity score–adjusted HR (95% CI)
LNG-IUD	48,599	78,363.7	128	1.05 (0.69, 1.57)	1.37 (0.90, 2.09)
Copper	11,429	18,565.4	28	1.00 (Reference)	1.00 (Reference)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.
Source: Analysis Table 18.16.1.

The study population with subsequent IUD insertions and IUD type available (those with unknown IUD type were removed) was included for this analysis. The number of all subsequent IUD insertions was only 60,510, compared with 326,658 first IUD insertions. The proportional hazards assumption was satisfied. Standardized differences prior to confounding adjustment were modest (Analysis Table 18.16.2.1 and Analysis Figure 18.16.1). After propensity score weighting, all of the variables included in the model had satisfactory balance (absolute standardized difference < 0.2) (Analysis Table 18.16.3.1 and Analysis Figure 18.16.1).

The HR point estimates were lower for the subsequent IUD insertions (crude HR, 1.05; adjusted HR, 1.37) than for the first insertions (crude HR, 1.34; adjusted HR, 1.49), and the 95% CIs for the subsequent insertions overlapped 1.0 for the comparison of LNG-IUDs versus copper IUDs.

10.5.13 Subsequent insertion analyses for breastfeeding, postpartum timing, and IUD type with IUD expulsion (objective 26)

Objective 26: To estimate the crude and adjusted HRs of IUD expulsion described in objectives 20 to 24 across all subsequent insertions (i.e., not the first insertion) observed within the data. (The site-specific analyses were performed only if there were more than 20,000 subsequent IUD insertions for that site. The pooled analysis included all sites regardless of the number of subsequent IUD insertions at a site.)

The crude incidence rates and cumulative incidence of IUD expulsion for all analyses of subsequent insertions (breastfeeding, postpartum timing, and IUD type) are in Additional Analysis Tables 8.10 through 8.12 provided in a stand-alone document (see list in Annex 1).

10.5.13.1 Breastfeeding and IUD expulsion—subsequent insertions

The crude HRs for IUD expulsion and breastfeeding status for subsequent IUD insertions are shown in Table 52. Pooled adjusted analyses were not reported due to the statistical interaction between breastfeeding status and research site. Adjusted analyses by site were not reported due to occurrence of fewer than 20,000 insertions at any site.

Table 52: Crude hazard ratios for IUD expulsion; subsequent IUD insertions, by breastfeeding status; pooled across research sites

Breastfeeding status	No. of insertions	Person-years	No. of events	Crude HR (95% CI)	Propensity score–adjusted HR[a] (95% CI)
Breastfeeding	9,772	16,659.2	246	0.54 (0.44, 0.65)	—
Not breastfeeding	4,311	7,033.2	192	1.00 (Reference)	—

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.
[a] Adjusted for propensity score.
Source: Analysis Table 26.20.1.

The crude analysis for subsequent IUD insertions was consistent with the trend for first IUD insertions, lower rates of IUD expulsion among women who were breastfeeding at the time of IUD insertion compared with those not breastfeeding at that time (crude HR, 0.54).

10.5.13.2 Postpartum timing and IUD expulsion—subsequent insertions

10.5.13.2.1 Four-category postpartum timing

The crude, propensity score–adjusted, and fully adjusted HRs for IUD expulsion with the four-category postpartum timing for subsequent IUD insertions are shown in Table 53 (pooled across research sites and stratified by postinsertion follow-up time ≤ 49 days and > 49 days after IUD insertion).

Table 53: Crude and adjusted hazard ratios for IUD expulsion for three categories of postpartum timing at IUD insertion compared with those who were more than 52 weeks postpartum or with no recorded delivery, stratified by post–IUD insertion time; pooled complete study population, all subsequent IUD insertions

Postpartum timing at IUD insertion	Events	Insertions	Person-years	Crude HR (95% CI)	Propensity score–adjusted[a] HR (95% CI)	Fully adjusted[b] HR (95% CI)
Within 49 days of IUD insertion						
≤ 6 weeks	27	3,298	426.8	0.65 (0.44, 0.96)	0.67 (0.43, 1.04)	0.92 (0.56, 1.51)
> 6 to ≤ 14 weeks	31	7,122	926.1	0.34 (0.24, 0.49)	0.45 (0.30, 0.68)	0.61 (0.39, 0.95)
> 14 to ≤ 52 weeks	75	3,976	509.8	1.51 (1.19, 1.92)	1.39 (1.01, 1.90)	1.61 (1.15, 2.23)
> 52 weeks or no delivery	580	46,114	5,966.8	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

Postpartum timing at IUD insertion	Events	Insertions	Person-years	Crude HR (95% CI)	Propensity score–adjusted[a] HR (95% CI)	Fully adjusted[b] HR (95% CI)
More than 49 days after IUD insertion						
≤ 6 weeks	73	3,057	4,672.2	0.89 (0.70, 1.12)	0.81 (0.61, 1.06)	1.12 (0.80, 1.56)
> 6 to ≤ 14 weeks	115	6,700	11,644.7	0.59 (0.49, 0.71)	0.70 (0.56, 0.87)	0.94 (0.70, 1.25)
> 14 to ≤ 52 weeks	128	3,612	6,103.1	1.26 (1.05, 1.52)	1.32 (1.05, 1.65)	1.53 (1.21, 1.94)
> 52 weeks or no delivery	1,175	42,897	67,454.0	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California.

[a] Adjusted for propensity score.

[b] Adjusted for propensity score and breastfeeding status.

Source: Analysis Table 26.23.1, pooled and by research site (KPNC and KPSC only), and Analysis Table 26.23.1a.

The complete study population with subsequent insertions was included in this analysis. The proportional hazards assumption was violated; therefore, a time-dependent interaction covariate, postpartum period by time (≤ 49 days from IUD insertion), was included in each Cox model. In the cohort with subsequent IUD insertions, pooled across research sites, the standardized differences prior to confounding adjustment were substantial (Analysis Table 26.23.2 and Analysis Figure 26.23.1). After propensity score weighting, most of the variables included in the model had satisfactory balance (absolute standardized difference < 0.2) (Analysis Table 26.23.3.1 and Analysis Figure 26.23.1). Among the variables included in propensity scores, the only exception was duration of look-back period > 6.5 years, which was marginally unbalanced. Breastfeeding could not be included in the propensity score model because in the > 52-week postpartum category, no woman was categorized as breastfeeding at the time of IUD insertion; breastfeeding status was included as a covariate separate from the propensity score model.

In the crude and propensity score–adjusted analyses, the IUD insertion group > 6 weeks to ≤ 14 weeks postpartum had a lower risk of IUD expulsion than the group with IUDs inserted > 52 weeks postpartum or with no recorded delivery in both the ≤ 49-day postinsertion time period (crude HR, 0.34; adjusted HR, 0.45) and the > 49-day postinsertion time period (crude HR, 0.59; adjusted HR, 0.70). After additional adjustment for breastfeeding status at IUD insertion, the risk of expulsion in the IUD insertion group > 6 weeks to ≤ 14 weeks postpartum remained significantly lower in the ≤ 49-day postinsertion time period (fully adjusted HR, 0.61), but was no longer significantly lower in the > 49-day follow-up time period (fully adjusted HR, 0.94). The risk of IUD expulsion in the IUD insertion group > 6 weeks to ≤ 14 weeks postpartum was also lower than in the other two early postpartum groups (≤ 6 weeks and > 14 to ≤ 52 weeks) in the crude, the propensity score–adjusted, and the fully adjusted analyses both within the first 49 days after insertion and more than 49 days after insertion. Compared with the group with IUDs inserted > 52 weeks postpartum or with no recorded delivery, the risk of IUD expulsion was significantly higher in the IUD insertion group > 14 to ≤ 52 weeks postpartum during both postinsertion time periods in the crude (≤ 49 days HR, 1.51; > 49 days HR, 1.26), propensity score–adjusted (≤ 49 days HR, 1.39; > 49 days HR, 1.32), and fully adjusted (≤ 49 days HR, 1.61; > 49 days HR, 1.53) analyses. Propensity score adjustment tended to increase all the HR point estimates, and additional adjustment for breastfeeding status increased the point estimates even more.

10.5.13.2.2 Postpartum cut point at 14 weeks

The crude, propensity score–adjusted and fully adjusted HRs for IUD expulsion in the groups with IUD insertion ≤ 14 weeks versus > 14 weeks postpartum, for subsequent IUD insertions, are shown in Table 54 (pooled).

Table 54: Crude, propensity score–adjusted, and fully adjusted hazard ratios for IUD expulsion for subsequent IUD insertion ≤ 14 weeks postpartum compared with > 14 weeks postpartum or with no recorded delivery; pooled complete study population, all subsequent IUD insertions

Weeks postpartum	No. of insertions	Person-years	No. of events	Crude HR (95% CI)	Propensity score–adjusted HR (95% CI)	Fully adjusted HR[a] (95% CI)
≤ 14	10,420	17,669.7	246	0.59 (0.51, 0.67)	0.66 (0.57, 0.76)	0.83 (0.64, 1.08)
> 14 or no delivery	50,090	80,033.7	1,958	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.
[a] Fully adjusted = adjusted for propensity scores and breastfeeding status.
Source: Analysis Table 26.21.1, pooled and by research site (KPNC and KPSC only).

The complete study population with subsequent IUD insertions was included in this analysis. The number of all subsequent IUD insertions was only 60,510, compared with 326,658 first IUD insertions. The proportional hazards assumption was determined to be met based on visual inspection of the of log-log survival curves. Standardized differences prior to confounding adjustment were substantial (Analysis Table 26.21.2 and Analysis Figure 26.21.1 [pooled]; Analysis Table 26.21.2 and Analysis Figures 26.21.2-26.21.3 [KPNC and KPSC]). After propensity score weighting, all of the variables included in the model had satisfactory balance (absolute standardized difference < 0.2) (Analysis Tables 26.21.3.1-26.21.3.3 and Analysis Figures 26.21.1-26.21.3). Breastfeeding was not included in the propensity score model, but breastfeeding status was included as a covariate separate from the propensity score model.

The HR point estimates for IUD expulsions comparing IUD insertion ≤ 14 weeks postpartum to > 14 weeks or no delivery recorded, pooled across sites, were lower for the subsequent IUD insertions (crude HR, 0.59; adjusted HR, 0.66; fully adjusted HR, 0.83) than first insertions (crude HR, 0.72; adjusted HR, 0.88; fully adjusted HR, not estimated). After adjusting for breastfeeding status at the time of IUD insertion, the 95% CI for subsequent insertions included the null value.

10.5.13.2.3 Postpartum cut point at 36 weeks

The crude, propensity score–adjusted, and fully adjusted HRs for IUD expulsion for subsequent IUD insertions ≤ 36 weeks postpartum versus > 36 weeks postpartum are shown in Table 55 (pooled).

Table 55: Crude, propensity score–adjusted, and fully adjusted hazard ratios for IUD expulsion for postpartum timing at subsequent IUD insertion ≤ 36 weeks compared with > 36 weeks postpartum or with no recorded delivery; pooled complete study population, all subsequent IUD insertions

Weeks postpartum	No. of insertions	Person-years	No. of events	Crude HR (95% CI)	Propensity score–adjusted HR (95% CI)	Fully adjusted HR[a] (95% CI)
≤ 36	13,160	22,270.1	384	0.74 (0.66, 0.83)	0.77 (0.67, 0.88)	1.18 (0.95, 1.45)
> 36 or no delivery	47,350	75,433.4	1,820	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device.
[a] Fully adjusted = adjusted for propensity scores and breastfeeding status.
Source: Analysis Table 26.22.1, pooled and by research site (KPNC and KPSC only).

The complete study population with subsequent IUD insertions was included in this analysis. The number of all subsequent IUD insertions was 60,510, compared with 326,658 first IUD insertions. The proportional hazards assumption was determined to be met based on visual inspection of the of log-log survival curves. Standardized differences prior to confounding adjustment were substantial (Analysis Table 26.22.2 and Analysis Figure 26.22.1 [pooled]; Analysis Table 26.22.2 and Analysis Figures 26.22.2-26.22.3 [KPNC and KPSC]). After propensity score weighting, all of the variables included in the model had satisfactory balance (absolute standardized difference < 0.2) (Analysis Tables 26.22.3.1-26.22.3.3 and Analysis Figures 26.22.1-26.22.3). Breastfeeding was not included in the propensity score model, but breastfeeding status was included as a covariate separate from the propensity score model.

The HR point estimates for data pooled across sites were slightly lower for subsequent IUD insertions (crude HR, 0.74; adjusted HR, 0.77; fully adjusted HR, 1.18) than those for first IUD insertions (crude HR, 0.76; adjusted HR, 0.95; fully adjusted HR, not estimated). Based on the crude and propensity score–adjusted HRs, there was a lower risk of IUD expulsion in the group with IUD insertion ≤ 36 weeks postpartum versus > 36 weeks postpartum or with no delivery recorded. After adjusting for breastfeeding status at the time of IUD insertion, the point estimate was 1.18 (higher risk of IUD expulsion with earlier postpartum insertion), but the 95% CI included the null value.

10.5.13.3 IUD type and IUD expulsion–subsequent insertions

The crude and propensity score–adjusted HRs for IUD expulsion for IUD type and subsequent IUD insertions are shown in Table 56.

Table 56: Crude and propensity score–adjusted hazard ratios for IUD expulsion for LNG-IUDs compared with copper IUDs; pooled across research sites, all subsequent IUD insertions

IUD type	No. of insertions	Person-years	No. of events	Crude HR (95% CI)	Propensity score–adjusted HR (95% CI)
LNG-IUD	48,599	78,363.7	1,652	0.70 (0.64, 0.78)	0.65 (0.58, 0.72)
Copper IUD	11,429	18,565.4	535	1.00 (Reference)	1.00 (Reference)

CI = confidence interval; HR = hazard ratio; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.
Source: Analysis Table 26.24.

The study population with subsequent IUD insertions and IUD type available was included in this analysis. The proportional hazards assumption was satisfied. In the cohort with subsequent IUD insertions pooled across research sites, the standardized differences prior to confounding adjustment were modest (Analysis Table 26.24.2 and Analysis Figure 26.24.1). After propensity score weighting, all of the variables included in the model had satisfactory balance (absolute standardized difference < 0.2) (Analysis Table 26.24.3.1 and Analysis Figure 26.24.1).

The crude and propensity score–adjusted HRs for IUD expulsion were lower for LNG-IUDs than for copper IUDs (crude HR, 0.70; adjusted HR, 0.65), and the point estimates for subsequent insertions were somewhat lower than those for first IUD insertions.

10.5.14 Indicators of potentially difficult IUD insertion (objective 13)

Objective 13: To describe the prevalence of indicators of a difficult IUD insertion (e.g., need for cervical dilation, ultrasound guidance, paracervical block, clinician not indicating difficulty, use of misoprostol among all users)

Table 57 summarizes the indicators of a potentially difficult insertion for the first IUD insertion in the pooled data, overall and by breastfeeding and postpartum timing of IUD insertion. Some indication of a potentially difficult insertion was seen in 9.1% of all IUD insertions. Women who were within 52 weeks postpartum, whether or not they were breastfeeding, had fewer indications of potentially difficult insertion (any indicator among 2.6% of insertions among women who were breastfeeding and 3.5% among those not breastfeeding). Those who were more than 52 weeks postpartum or had no delivery had more indicators of potentially difficult insertion (11.7%).

The indicators of potentially difficult insertion are not mutually exclusive (women could have had more than one of these indicators); therefore, the total over all the indicators may not equal the sum of individual indicators. Paracervical block was noted most frequently (4.5% of all IUD insertions) in all categories of breastfeeding and postpartum timing of IUD insertion.

Table 57: Indicators of a potentially difficult insertion, overall, by breastfeeding status, and by postpartum timing of IUD insertion; pooled, first observed IUD insertions

Difficult insertion indicator	All events	Breastfeeding		Postpartum timing of IUD insertion			
		Yes	No	6 weeks or less	> 6 to ≤ 14 weeks	> 14 to ≤ 52 weeks	> 52 weeks or no delivery
(N)	326,658	64,186	30,631	20,060	56,047	21,717	228,834
Cervical dilation, n (%)	10,209 (3.1)	279 (0.4)	396 (1.3)	108 (0.5)	205 (0.4)	441 (2.0)	9,455 (4.1)
Ultrasound guidance, n (%)	4,628 (1.4)	265 (0.4)	273 (0.9)	86 (0.4)	183 (0.3)	313 (1.4)	4,046 (1.8)
Paracervical block, n (%)	14,731 (4.5)	829 (1.3)	556 (1.8)	245 (1.2)	537 (1.0)	669 (3.1)	13,280 (5.8)
Provider note, n (%)	2,987 (0.9)	252 (0.4)	152 (0.5)	83 (0.4)	248 (0.4)	98 (0.5)	2,558 (1.1)
Use of misoprostol, n (%)	8,689 (2.7)	264 (0.4)	244 (0.8)	95 (0.5)	185 (0.3)	277 (1.3)	8,132 (3.6)
Any indicator, n (%)	29,777 (9.1)	1,686 (2.6)	1,077 (3.5)	573 (2.9)	1,261 (2.2)	1,146 (5.3)	26,797 (11.7)

IUD = intrauterine device.
Source: Analysis Table 13.1 (pooled data).

Table 58 summarizes the indicators of potentially difficult insertion for the first IUD insertion in the pooled data, overall and by IUD type and menorrhagia status. A lower percentage of women with copper IUD insertions had indicators of potentially difficult insertion than women with LNG-IUD insertions, and a lower percentage of women without menorrhagia had indicators of potentially difficult IUD insertion than those with menorrhagia. Paracervical block was noted most frequently in all categories of IUD type and menorrhagia status.

Table 58: Indicators of a potentially difficult insertion, overall, by IUD type and by menorrhagia status; pooled, first observed IUD insertions

	All events	IUD type		Menorrhagia in the past year	
		LNG-IUD	Copper	Yes	No
Total insertions, N	326,658	259,234	63,664	32,552	294,106
Difficult insertion indicator					
Cervical dilation, n (%)	10,209 (3.1)	8,730 (3.4)	1,356 (2.1)	1,373 (4.2)	8,836 (3.0)
Ultrasound guidance, n (%)	4,628 (1.4)	4,008 (1.5)	537 (0.8)	252 (0.8)	4,376 (1.5)
Paracervical block, n (%)	14,731 (4.5)	12,239 (4.7)	2,384 (3.7)	1,742 (5.4)	12,989 (4.4)
Provider note, n (%)	2,987 (0.9)	2,463 (1.0)	482 (0.8)	421 (1.3)	2,566 (0.9)
Use of misoprostol, n (%)	8,689 (2.7)	7,066 (2.7)	1,444 (2.3)	991 (3.0)	7,698 (2.6)
Any indicator, n (%)	29,777 (9.1)	24,666 (9.5)	4,648 (7.3)	3,754 (11.5)	26,023 (8.8)

IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system.
Source: Analysis Table 13.1 (pooled data).

Table 59 summarizes the indicators of potentially difficult insertion for the first IUD insertion in the pooled data and by research site. The proportion of these indicators was highest at RI, where more reliance was placed on review of clinical notes, and lowest at KPSC, where diagnosis coding was used more often for identifying potentially difficult insertions. The indicators of potentially difficult insertion varied by site. Paracervical block was noted most frequently at KPNC, use of misoprostol at KPSC and KPWA, and cervical dilation at RI.

Table 59: Indicators of a potentially difficult insertion; pooled and by site, first observed IUD insertions

	Pooled	KPNC	KPSC	KPWA	RI
Number of women	326,658	161,442	123,214	20,526	21,476
Difficult insertion indicator					
Any difficult insertion, n (%)	29,777 (9.1)	19,685 (12.2)	4,273 (3.5)	2,324 (11.3)	3,495 (16.3)
Cervical dilation, n (%)	10,209 (3.1)	8,501 (5.3)	33 (0.0)	102 (0.5)	1,573 (7.3)
Ultrasound guidance, n (%)	4,628 (1.4)	3,620 (2.2)	252 (0.2)	194 (0.9)	562 (2.6)
Paracervical block, n (%)	14,731 (4.5)	12,788 (7.9)	1,051 (0.9)	654 (3.2)	238 (1.1)
Difficult insertion noted, n (%)	2,987 (0.9)	1,701 (1.1)	767 (0.6)	230 (1.1)	289 (1.3)
Use of misoprostol, n (%)	8,689 (2.7)	3,827 (2.4)	2,329 (1.9)	1,295 (6.3)	1,238 (5.8)

IUD = intrauterine device; KPNC = Kaiser Permanente Northern California; KPSC = Kaiser Permanente Southern California; KPWA = Kaiser Permanente Washington; RI = Regenstrief Institute.
Source: Analysis Tables 13.2 through 13.5.

10.6 Adverse events/adverse reactions

This research study used secondary data from which personal identifiers were removed. The outcomes of uterine perforation and IUD expulsion are reported in the study results. Based on current guidelines from ISPE [23] and the EMA [25], noninterventional studies conducted using electronic claims and health care records do not require reporting of adverse events or reactions.

11. Discussion

11.1 Key results

This study was designed to evaluate in a US population whether the risk of uterine perforation differed if IUDs were inserted in the early postpartum time period, a practice that is currently recommended by the American College of Obstetricians and Gynecologists in the US to reduce the risk of unintended and short-interval pregnancies [26], and whether risk of uterine perforation was different depending on whether women were breastfeeding at the time of IUD insertion. The magnitude of the interaction between breastfeeding status and postpartum timing of IUD insertion for risk of uterine perforation was also of interest. These concerns of the FDA arose from results of the prospective observational study EURAS-IUD [2] and an interest in understanding whether the risks associated with earlier postpartum IUD insertion and breastfeeding at the time of insertion seen in EURAS-IUD would be different in a US population given differences in IUD insertion practices.

Additional questions addressed in this study included risk of IUD expulsion with breastfeeding status, postpartum timing of IUD insertion, type of IUD, and recent menorrhagia diagnosis (i.e., within 12 months before IUD insertion); risk of uterine perforation with IUD type and recent menorrhagia diagnosis; and whether the risks associated with postpartum timing and breastfeeding differ by IUD type (LNG versus copper) for both uterine perforation and IUD expulsion outcomes.

In this cohort study conducted in the setting of three health care systems and one health information exchange with EHRs, we identified 326,658 women, aged 50 years or younger, with at least one IUD insertion. The average age in this population was 32 years, and across the four research sites, the population was racially and ethnically diverse. The women included in this study at each site reflected the general populations in the geographic regions from which they were drawn.

The incidence of uterine perforation and IUD expulsion was evaluated in three different study populations, (complete study population, women with breastfeeding status information and within 52 weeks postpartum at IUD insertion, and women with information on IUD type). The incidence of uterine perforation was higher in the study population comprising women with breastfeeding status information who were ≤ 52 weeks postpartum at the time of IUD insertion than in the complete study population and in the population of women with information on IUD type available (the incidence of uterine perforation was essentially the same in the latter two populations). In contrast, the population with breastfeeding status and IUD insertion at ≤ 52 weeks postpartum had a lower incidence of IUD expulsion than the other two study populations.

11.1.1 Association of breastfeeding and postpartum timing of IUD insertion with uterine perforation

The two primary objectives focused on the risk of uterine perforation associated with breastfeeding status and postpartum timing of IUD insertion. There was about a 40% higher risk of uterine perforation among women within 52 weeks postpartum who were breastfeeding at the time of IUD insertion versus those who were not breastfeeding (adjusted HR, 1.37). The point estimates differed across the sites, which might be related to differences in how breastfeeding status at IUD insertion was identified, with some using linkage to well-child visits for the infant and others using data from the woman's chart either for postpartum visits or on the date of IUD insertion. However, the incidence rates and cumulative incidence for uterine perforation by breastfeeding status were generally consistent across sites.

Risk of uterine perforation was also higher among women with IUD insertion within the first 52 weeks postpartum than in women who were more than 52 weeks postpartum or with no recorded delivery in the previous year (including nulliparous women). Regardless of the cut points that were used to define "early postpartum" IUD insertions (i.e., 6 weeks, 14 weeks, 36 weeks) the earlier postpartum time period had a higher risk of uterine perforation than the referent group (later postpartum or with no recorded delivery, including nulliparous women).

We divided the IUD insertions within the first 52 weeks postpartum into three categories for postpartum time of IUD insertion, adjusted the analysis for propensity score and breastfeeding status, and then compared each postpartum category with women who had an IUD insertion more than 52 weeks postpartum or had no recorded delivery. The results showed a clear pattern in the adjusted HRs for uterine perforation across these categories of postpartum time of IUD insertion: ≤ 6 weeks, 6.29; 6 to ≤ 14 weeks, 4.65, and 14 to ≤ 52 weeks, 2.94. However, we suspected significant heterogeneity in the earliest postpartum category (≤ 6 weeks), so we further divided that group into IUD insertion 0 to 3 days postpartum and 4 days to ≤ 6 weeks postpartum. With these categories, the risk of uterine perforation in women with IUDs inserted in the immediate postpartum period (0-3 days) compared with women with IUDs inserted > 52 weeks postpartum or with no recorded delivery still had a higher risk of uterine perforation (adjusted HR, 2.73); however, it was lower than the risk observed for women with an IUD insertion in the period 4 days to ≤ 6 weeks postpartum (adjusted HR, 6.71). These results suggest that IUD insertions done within the first 3 days after delivery are less likely to result in a uterine perforation than those done in a later postpartum time period (especially 4 days to 14 weeks postpartum).

In the primary analyses, we allowed an extra 3 months beyond the labeled expiration of IUDs (e.g., for Mirena the censoring based on IUD expiration was 5 years and 3 months) because of the understanding that some perforations are not recognized until women return to have the IUD removed or replaced, and not all women return before or on the IUD expiration date. However, the

clinicians on the research team also recognized that IUDs may currently be used beyond their original labeled expirations (e.g., Mirena may be used for 7 years rather than 5 years). Therefore, we conducted a sensitivity analysis that extended the censoring based on IUD expiration for an additional 2 years for all IUDs. The results of this sensitivity analysis were comparable to those from the original analysis.

Another finding relates to the interaction between breastfeeding status and postpartum timing of IUD insertion. There was a statistically significant ($P = 0.023$) departure from a multiplicative relation between breastfeeding status and postpartum timing of IUD insertion for risk of uterine perforation. Both earlier postpartum IUD insertion and breastfeeding were associated with a higher risk of uterine perforation, and the lowest risk was seen in those with later postpartum timing of IUD insertion who were not breastfeeding. Compared with women with IUD insertions > 14 to ≤ 52 weeks postpartum who were not breastfeeding, risk of uterine perforation was highest in those with IUD insertions ≤ 14 weeks postpartum who were breastfeeding (adjusted HR, 3.28), followed by those with IUD insertions ≤ 14 weeks postpartum who were not breastfeeding (adjusted HR, 2.56) and those with IUD insertions > 14 to ≤ 52 weeks postpartum who were breastfeeding (adjusted HR, 2.41). Similarly, the incidence rates for these categories of breastfeeding and postpartum timing are logical, with the highest incidence rate in those with IUD insertions ≤ 14 weeks postpartum who were breastfeeding (crude incidence, 4.37 per 1,000 person-years), followed by those with IUD insertions > 14 to ≤ 52 weeks postpartum who were breastfeeding (crude incidence, 3.40 per 1,000 person-years) and those with IUD insertions ≤ 14 weeks postpartum who were not breastfeeding (crude incidence, 3.30 per 1,000 person-years) and then those with IUD insertions > 14 to ≤ 52 weeks postpartum who were not breastfeeding (crude incidence, 1.17 per 1,000 person-years).

In an analysis that used a 36-week cut point to define earlier postpartum IUD insertions (same cut point as EURAS-IUD), the adjusted overall IRR for uterine perforation at 1 and 5 years of follow-up was higher for those with IUD insertions ≤ 36 weeks postpartum versus those with IUD insertions > 36 weeks or with no recorded delivery. However, among women who were breastfeeding, the risk of uterine perforation associated with postpartum IUD insertion ≤ 36 weeks was similar to the risk for those with insertion > 36 weeks. The higher risk with earlier postpartum IUD insertions (≤ 36 weeks postpartum) relative to insertions later postpartum or with no recorded delivery was only evident in those who were not breastfeeding. In that same analysis, we calculated IRDs and found that, overall, there were an additional 3.75 perforations per 1,000 person-years at 1 year and 2.28 at 5 years among those with IUD insertions earlier postpartum compared with later postpartum or no recorded delivery overall. The higher rate difference in perforations in the earlier postpartum insertion group compared with the later postpartum time was confined to those who were not breastfeeding (3.92 more perforations per 1,000 person-years at 1 year and 2.33 at 5 years). These results are consistent with the formal statistical interaction found using HRs and a 14-week cut point.

In EURAS-IUD, the relative risk of uterine perforation associated with breastfeeding versus not breastfeeding at the time of IUD insertion was 3.3 in the earlier postpartum time period (≤ 36 weeks postpartum at the time of IUD insertion) and 2.2 in the later postpartum group (> 36 weeks postpartum at IUD insertion) [2]. In APEX IUD, the adjusted hazard ratio for uterine perforation associated with breastfeeding at IUD insertion was 1.3 in the earlier postpartum time period (≤ 14 weeks at the time of IUD insertion) and 2.4in the later postpartum group (> 14 weeks postpartum at IUD insertion). The risk associated with breastfeeding at the time of IUD insertion in the later postpartum time period for the two studies was similar (2.2 in EURAS-IUD and 2.4 in

APEX IUD), but the risk associated with breastfeeding in the earlier postpartum time period was higher in EURAS-IUD (RR, 3.3) than in APEX IUD (adjusted HR, 1.3). Differences in the definition of earlier postpartum time periods for this stratified analysis and differences in the variables included for adjustment of confounding could have contributed to differences in the risk associated with breastfeeding. Also, misclassification of breastfeeding status is more likely in APEX IUD, which could also contribute to the lower risk associated with breastfeeding at IUD insertion in APEX IUD. However, both studies provide evidence that both breastfeeding at IUD insertion and earlier postpartum IUD insertions are risk factors for uterine perforation.

11.1.2 Association of breastfeeding and postpartum timing of IUD insertion with IUD expulsion

In the propensity score–adjusted analysis, among women who were ≤ 52 weeks postpartum at the time of IUD insertion, results showed about a 30% lower risk of IUD expulsion among women who were breastfeeding at the time of IUD insertion versus those who were not breastfeeding. The point estimates varied quite a lot across the sites; after propensity score adjustment, the risk of IUD expulsion was 50%-60% lower at KPSC and KPWA. At KPNC, the point estimate was about 10% lower, but the 95% CI overlapped the null value, and at RI, the point estimate was about 20% higher but the 95% CI overlapped the null value. As described previously and in the limitations section (Section 11.2), the different approaches used to ascertain breastfeeding status might have led to the wide range of risk estimates observed at some sites.

The findings of the current study are consistent with results reported in a systematic review by Berry-Bibee et al. [27]. This review included five studies that reported on risk of IUD expulsion with breastfeeding at the time of IUD insertion; one study reported a lower rate of expulsion among women who were breastfeeding at IUD insertion, three studies reported no significant difference in rate of expulsion in those breastfeeding versus those not breastfeeding, and one study reported a lower rate with breastfeeding if the women were 6 to 12 weeks postpartum at the time of insertion and a higher rate with breastfeeding if they were 4 to 12 months postpartum at the time of IUD insertion.

In the current study, risk of IUD expulsion was somewhat lower among women with IUD insertion within the first 52 weeks postpartum compared with women who were more than 52 weeks postpartum or with no recorded delivery (including nulliparous women). However, this risk varied depending on the cut points used to define earlier postpartum IUD insertions and was attenuated when adjusting for breastfeeding status, suggesting a significant amount of confounding by breastfeeding.

When we divided the insertions within the first 52 weeks postpartum into three categories, adjusted for propensity score, then compared with women more than 52 weeks postpartum or with no recorded delivery in the previous 12 months at the time of IUD insertion, only those with IUD insertion > 6 to ≤ 14 weeks postpartum had an appreciably lower risk of IUD expulsion both before and after 49 days of IUD insertion; after adjustment for breastfeeding status, this risk was largely attenuated. We suspected substantial heterogeneity in the earliest postpartum category (≤ 6 weeks), so we further divided that group into IUD insertion 0 to 3 days postpartum and 4 days to ≤ 6 weeks postpartum. The risk of IUD expulsion in women with IUDs inserted in the immediate postpartum period (0-3 days) was much higher (fully adjusted HR, 5.34) than in those with IUD insertion 4 days to ≤ 6 weeks postpartum (fully adjusted HR, 1.22) when each group was compared with women with IUDs inserted > 52 weeks postpartum or with no recorded delivery. After this further stratification of the earlier postpartum time period, the risk of IUD expulsion when the IUD was

inserted 4 days to ≤ 6 weeks postpartum (fully adjusted HR, 1.22) was comparable to the risk when the IUD was inserted > 6 to ≤ 14 weeks postpartum (fully adjusted HR, 1.06).

Although we did not do a formal test for interaction between breastfeeding status and postpartum timing of IUD insertion for risk of IUD expulsion, in the analysis that used the 36-week cut point (Section 10.5.6.5), we observed that the risk of IUD expulsion for IUD insertions ≤ 36 weeks postpartum compared with insertions > 36 weeks postpartum or with no recorded delivery was lower only for women who were breastfeeding and only at 1 year of follow-up (adjusted IRR, 0.60). We also calculated incidence rate differences and found that, overall, there were an additional 4.3 IUD expulsions per 1,000 person-years at 1 year and 2.4 per 1,000 person-years at 5 years among those with IUD insertions earlier postpartum (≤ 36 weeks) compared with IUD insertions later postpartum or with no recorded delivery. However, in those who were breastfeeding, there were 10.8 per 1,000 person-years *fewer* expulsions in the earlier postpartum group (≤ 36 weeks) than in the later postpartum group at 1 year. In those who were not breastfeeding, there were 5.1 per 1,000 person-years *more* expulsions at 1 year in the earlier postpartum group than in the later postpartum group. These results suggest an important influence of breastfeeding status on IUD insertion timing for the IUD expulsion outcome.

As described in reviews by Whitaker and Chen [28] and Jatlaoui et al. [29], the rates of IUD expulsion in the literature are quite variable and differed by postpartum timing, vaginal versus cesarean delivery, and IUD type. The rates we report here were lower, but also varied depending on postpartum timing of IUD insertion, breastfeeding status, and presence or absence of menorrhagia.

11.1.3 Association of IUD type with uterine perforation and IUD expulsion

The results of all analyses with IUD type are not stratified by research site, in compliance with the Data Use Agreement with Kaiser Permanente, because of a concern from the KP sites about release of information on the volume of use of specific IUD brands and because Bayer was the sole sponsor of this study, but not the only marketing authorization holder of the all the IUD brands included in this study. Inclusion of data from RI, a non-KP site, offered sufficient masking to allay this concern on the part of KP for reporting results of pooled data.

The risk of uterine perforation was approximately 50% higher for women receiving LNG-IUDs than for those receiving copper IUDs (adjusted HR, 1.49). The crude cumulative incidence at 1 year was 2.2 per 1,000 at risk for those receiving LNG-IUDs and 1.6 per 1,000 for those receiving copper IUDs; at 5 years, the crude cumulative incidence was 6.3 per 1,000 person-years of observation for LNG-IUDs and 5.5 per 1,000 for copper IUDs. These results are similar to those from EURAS-IUD, which found a small absolute difference in perforation rates between IUD types and a 60% higher risk of uterine perforation among women receiving LNG-IUDs versus copper IUDs at 1 year of follow-up [2]. The crude incidence of uterine perforation over 1 year of follow-up in EURAS-IUD was 1.4 per 1,000 insertions among those receiving LNG-IUDs and 1.1 per 1,000 insertions for copper IUDs [2]. In EURAS-IUD, they followed 39,009 of the original study population of 61,448 women for up to 5 years and reported a perforation incidence of 2.1 per 1,000 insertions in the LNG-IUD group and 1.6 per 1,000 insertions in the copper IUD group [30]. While there were differences between the two studies in the approach to collection of data on this outcome (medical records in APEX IUD versus self-report with confirmation by the physician in EURAS-IUD) and differences in the calculation of incidence (estimated from Kaplan-Meier curves for APEX IUD and incidence per 1,000 insertions in EURAS-IUD), the conclusion of modestly higher risk of uterine perforation with LNG-IUDs versus copper IUDs (50% in APEX IUD and 60% in EURAS-IUD) is consistent, even though the incidence rates are low in both studies. The Kaplan-Meier curve for

LNG-IUDs shows an uptick right around 5-years of follow-up, which might be due to perforations that are detected at the time women are returning to their physician to have the IUD removed. APEX IUD did not have sufficient numbers of women followed for 10 years to determine whether there is a similar uptick for the copper IUDs when women returned for removal of copper IUDs.

For IUD expulsion, the crude incidence and cumulative incidence at 1 year were quite similar between those with an LNG-IUD and those with a copper IUD. The cumulative incidence curves (Figure 28) are nearly indistinguishable up through about 1.5 years after insertion. After that time, they diverge a bit, with the cumulative incidence of IUD expulsion for those with an LNG-IUD slightly lower than for those with a copper IUD through 5 years after insertion. Similarly, the crude HR (0.96) had a 95% CI that included the null value. After adjustment for confounding, the risk of IUD expulsion with LNG-IUDs was about 30% lower than for copper IUDs (adjusted HR, 0.69). Because Mirena (which constitutes the largest proportion of the LNG-IUDs) has an indication (secondary to contraception) for menorrhagia (i.e., heavy menstrual bleeding) that none of the other IUDs have, and the risk of IUD expulsion is very high for women with menorrhagia, it is possible that menorrhagia is an important contributor to confounding in the crude estimate that was addressed with propensity score adjustment. It is also possible that women are more likely to notice and report to their physician the expulsion of an LNG-IUD because menstrual bleeding would likely return while there would be no such trigger for women with a copper IUD.

11.1.4 Association of menorrhagia with uterine perforation and IUD expulsion

The crude incidence and cumulative incidence of uterine perforation in the complete study population (pooled and at each site) was lower in women with a recent diagnosis of menorrhagia, resulting in a 40% lower risk (HR, 0.61). However, after propensity score adjustment, the risk of uterine perforation among women with a diagnosis of menorrhagia in the 12 months before IUD insertion was about 40% higher (adjusted HR, 1.38) than for women without that diagnosis in the complete study population. The large change in the crude versus adjusted HRs after adjustment for propensity scores indicated a large amount of confounding in the association between menorrhagia and uterine perforation.

The clinicians on the study team recommended that we confine this analysis to women who were more than 52 weeks postpartum (including those with no recorded delivery) at the time of IUD insertion because menorrhagia was much less likely to be diagnosed in those who had recently given birth. Therefore, we conducted an additional analysis excluding women with a delivery in the previous 52 weeks. In this study population, the crude incidence and cumulative incidence estimates of uterine perforation were low (crude incidence rate less than 1 per 1,000 person-years of observation), but were slightly higher in the women with a recent diagnosis of menorrhagia than in those without the diagnosis (pooled and at all sites). The crude and adjusted HRs in this study population were very similar (crude HR, 1.54; adjusted HR, 1.53), so we concluded that the women who had given birth in the previous 52 weeks were introducing significant heterogeneity, which resulted in confounded crude estimates. However, the adjusted HR in the larger population that included women who had delivered in the previous 12 months (1.38) was similar to the adjusted HR in the subpopulation without a delivery in the previous 52 weeks (1.53), so the adjustment for confounding seemed adequate.

For IUD expulsion, in the complete study population, the crude incidence rate and 1-year and 5-year cumulative incidence were much higher for women with a diagnosis of menorrhagia in the previous 12 months than in those without this diagnosis in the previous 12 months (pooled and at each site). The adjusted HR for the pooled study population was 2.79. At each site, a recent menorrhagia

diagnosis was associated with a higher crude HR (KPNC, 3.56; KPSC, 4.13; KPWA, 2.17; RI, 2.88); propensity score adjustment somewhat attenuated the estimates (KPNC, 2.92; KPSC, 2.81; KPWA, 1.79; RI, 2.25), although the lower bound of the 95% CIs still excluded the null value.

With the same rationale as described previously, we conducted an additional analysis that excluded women who were within 52 weeks postpartum. The crude incidence rates and cumulative incidence of IUD expulsion at 1 year and 5 years of follow-up were virtually the same as in the complete study population and, as expected, the crude HRs in the study population that excluded women who had delivery in the previous 52 weeks were very similar to those in the complete study population. After adjustment, the HRs were again somewhat attenuated compared with the crude HRs, but the risk of IUD expulsion associated with a diagnosis of menorrhagia was still elevated compared with those without this diagnosis (adjusted HRs: pooled, 2.84; KPNC, 2.97; KPSC, 2.85; KPWA, 1.82; RI, 2.34).

The results from this study suggest a higher risk of both uterine perforation and IUD expulsion in women with a diagnosis of menorrhagia in the 12 months before IUD insertion than in those without such a diagnosis. We could not identify any published studies that reported the risk of uterine perforation among women with menorrhagia versus those without. Studies that have reported on the risk of IUD expulsion with menorrhagia have consistently reported a higher risk of expulsion among women with menorrhagia [31-33].

11.1.5 Influence of interactions of IUD type with breastfeeding and with postpartum timing of IUD insertion on risk of uterine perforation and IUD expulsion

None of the tests for statistical interaction of IUD type with breastfeeding status or with postpartum timing of IUD insertion for either uterine perforation or IUD expulsion were significant. Therefore, the main effects of IUD type, breastfeeding status, and postpartum timing of IUD insertion are appropriate estimates of the risk of uterine perforation and IUD expulsion.

11.1.6 Indicators of difficult insertions

We included five indicators that might be indicative of a difficult IUD insertion: cervical dilation, ultrasound use, paracervical block, use of misoprostol, and difficult insertion noted in the clinical notes. Admittedly, if any of the four procedures were used prophylactically, they might have made the insertion easier, and we are unable to determine whether the procedures/medications were used preventatively or as a result of encountered difficulty at the time of insertion or due to a history of difficult insertion. Across the sites, 9.1% of the first IUD insertions had at least one of these indicators at the time of the insertion. The proportion of insertions with one of these indicators varied across the sites: 12.2% of the insertions at KPNC, 3.5% at KPSC, 11.3% at KPWA, and 16.3% at RI. Among women who were within 52 weeks postpartum and breastfeeding, 2.6% had one of these indicators, while in those who were not breastfeeding but also within 52 weeks postpartum, 3.5% had an indicator. Insertions that were done in the earlier postpartum time periods generally had a lower prevalence of one of these indicators: 2.9% for ≤ 6 weeks postpartum, 2.2% for > 6 to ≤ 14 weeks postpartum, 5.3% for > 14 to ≤ 52 weeks postpartum, and 11.7% for > 52 weeks postpartum (or with no recorded delivery). Among women receiving copper IUDs, 7.3% had one of these indicators, while 9.5% of those receiving an LNG-IUD had an indicator. Among women with a recent menorrhagia diagnosis, 11.5% had one of these indicators, and 8.8% of those without a recent menorrhagia diagnosis had one of these indicators.

11.2 Limitations

As with any observational study, unmeasured differences between the treatment groups may have affected the risk of outcomes. Use of propensity scores and use of overlap weights for the relative comparison and adjusting the HRs for potential confounders helped to reduce this source of bias, but the possibility of residual confounding persisted, which would have affected calculated point estimates, 95% CIs, and *P* values. Unmeasured confounding could result in incorrect findings in the comparison of defined cohorts. That said, an unmeasured confounder would have had to have been very unbalanced between cohorts to have a large impact on the outcomes due to the sheer numbers in this study.

As with any health care system data source used for secondary data analysis, data were not available before the enrollment date of the individual. Thus, data were not available regarding use of an IUD, pregnancy, or baseline covariates prior to enrollment. A minimum 12-month look-back period prior to IUD insertion was required for inclusion in the study population, but all available time in the health care plan prior to IUD insertion was used to improve the assessment of potential confounders [11].

Hypothesis testing was planned for the effects of breastfeeding at the time of IUD insertion and timing of postpartum IUD insertion on the outcome of uterine perforation. No adjustment for multiplicity was planned. Adjustment for multiplicity either recalculates the probabilities or adjusts the interpretation from a statistical test to control against type I error (i.e., false-positive, the statistical test is “significant” when the null hypothesis is true). However, adjustment for multiplicity can increase the type II error (i.e., false-negative, the statistical test is “significant” when the null hypothesis is false). A balance between type I and type II error is particularly important when the research question addresses a safety outcome. In this case, we did not adjust for multiplicity because we did not want to increase the possibility of *finding* no increased risk of uterine perforation *if* there were in fact an actual increased risk of uterine perforation associated with either breastfeeding at the time of IUD insertion or postpartum timing of IUD insertion.

Propensity scores were used to measure the probability of being “exposed” given specified covariates. The propensity scores were developed with respect to the outcomes being assessed within this study and thus were not outcome-blinded. This is a variable selection technique that elicits good results for propensity score models [16].

The results of this study were dependent on accurate capture of data and definitions of variables. Since variables were determined from diagnosis codes (ICD-9-CM, ICD-10-CM‡‡), Current Procedural Terminology codes, medication codes (National Drug Codes), and clinical notes (i.e., via NLP) there was a possibility of misclassification. Algorithms for the outcome variables, uterine perforation and IUD expulsion, had been validated in these four data sources prior to use of 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 rates of these outcomes were reviewed prior to and after the implementation of ICD-10-CM coding to ensure consistency over time. For variables that had not been validated in these data sources, algorithms validated in other data sources (e.g., administrative claims) were used to identify conditions and medication

‡‡ ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification;*
ICD-10-CM = *International Classification of Diseases, 10th Revision, Clinical Modification.*

dispensing, when available. In addition, the study team developed and shared conceptual definitions across data sources to standardize approaches to data capture.

There was potential for underreporting of outcomes within the data sources since women would need to seek treatment in order to have an outcome diagnosed. Asymptomatic perforation or IUD expulsion may not have been captured. In addition, there may have been a lag time between the occurrence of perforation or IUD expulsion and the time that the woman sought treatment. Thus, the occurrence of outcomes may have been missed. However, this approach was representative of the way that these outcomes would appear within clinical practice and is similar to that used in EURAS-IUD. Also, there was no reason to believe that underreporting of outcomes would differ by breastfeeding status (yes/no), postpartum timing, or menorrhagia diagnosis (yes/no). Importantly, the outcomes for IUD type might be captured differentially because very few women were available for the study for the full 10-years until expiration of a copper IUD, and expulsion of LNG-IUDs might be recognized more often because of the menstrual bleeding that might return. The absolute incidence rates may not have been entirely accurate because of potential underestimation due to underreporting or inaccurate coding or our inclusive definition of the outcomes. However, the HRs should provide an unbiased estimate of any differential risk between exposure groups (e.g., breastfeeding status [yes/no], earlier postpartum timing of IUD insertion vs. insertion > 52 weeks postpartum, menorrhagia status [yes/no], postpartum timing of IUD insertion x breastfeeding status). This might not have been true of HR estimates for IUD type. We also assessed rates of uterine perforation and IUD expulsion in the literature to provide an external context for the incidence rates estimated in this study.

While the duration of use of copper IUDs (up to 10 years) was beyond the duration of follow-up at two of the sites, the analyses that compared copper and LNG-IUDs only included time for which there is data for both types. Even so, this might have led to an overestimation of outcomes for LNG-IUDs because many more women would have returned for an IUD removal/replacement visit than was possible for women with copper IUDs during the duration of this study.

There was potential for misclassification and missingness of breastfeeding status at the time of IUD insertion. The research sites obtained information for this variable in different ways: at KPNC and KPSC, a structured questionnaire that captured breastfeeding status at infant check-ups was used. Although this provided nearly complete data on breastfeeding status (breastfeeding status could not be determined for only 0.9% at KPSC and 1.3% at KPNC among women within 52 weeks postpartum at IUD insertion), the IUD insertion might have been done between visits at which information about breastfeeding was obtained, so some misclassification may have occurred. RI used an NLP algorithm to identify breastfeeding status (yes and no) and had a larger proportion of women for whom breastfeeding status could not be determined (21.6% of those within 52 weeks postpartum). KPWA reviewed the electronic records to ascertain breastfeeding status, and breastfeeding status could not be determined for about 17% of those within 52 weeks postpartum; however, for the remainder, the likelihood of misclassification might have been lower. The complexity of identifying information on breastfeeding status within the charts was somewhat mitigated through the involvement of both clinicians and seasoned data informaticists working within each health care system who had experience with identifying such information. Further, the classification of breastfeeding as yes or no was a crude dichotomy and did not follow the potential biological mechanism for breastfeeding to affect uterine perforation or IUD expulsion. For example, breastfeeding once per day differs from eight times per day (the recommendation from one research partner to have a meaningful biologic change in reproductive hormone and potential effect on

tissues), and thus combining all breastfeeding into one category combined a heterogeneous experience.

The complexity of the US health care environment and changes in treatment patterns over calendar time mean that there was potential for differences across health care systems to occur due to the different starting times for each health care system. Calendar time was included in the propensity score.

Most of the data were from west coast health care systems, with just one health care system from the central US, but there was considerable diversity in factors such as race/ethnicity within each health care system. Further, in the validation study, there were no significant differences in the study population characteristics or outcome prevalence across these health care systems.

Because the data used by RI are not from a comprehensive health care system, there is some possibility that women who received their IUD in a hospital setting (e.g., after delivery) and then returned to their personal physician for clinical care might have been lost to follow-up after the IUD insertion if the clinical practice did not contribute to the health information exchange. Therefore, the lower rates of uterine perforation and IUD expulsion in the earliest postpartum timing group ($\leq$ 6 weeks or 0-3 days) might reflect this loss to follow-up. Also, concomitant gynecological procedures are not required fields in the Indiana Health Information Exchange, so lower rates at RI may reflect incomplete data.

The uterine perforation and IUD expulsion outcome definitions that we used included both complete and partial outcomes. This was the approach we used for validation of the algorithms, and we wanted to use this inclusive definition in this safety study. However, we recognize that the clinical consequences of complete versus partial perforations can be quite different, complete perforations most likely have to be removed in the operating room via intra-abdominal surgeries with risk to bowel, bladder, and large vessels, while partial perforations are more likely to be able to be removed in a physician's office and are very low risk. Similarly, partial expulsions might still be effective for contraception, while complete expulsions put a woman at risk of an unanticipated pregnancy. Reviewers at each site evaluated whether perforations were complete or partial and the certainty of their decision regarding completeness of the perforation. Across all sites, only about 50% of the perforations were judged to be complete. Among the sites that reported on complete versus partial expulsion, only 48% were determined to be complete. Thus, the incidence rates might be an overestimate of these outcomes, but the risk estimates (hazard ratios and incidence rate ratios) should be unbiased estimates of the associations of outcomes with the exposures.

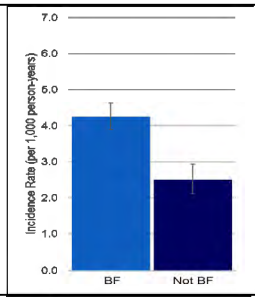
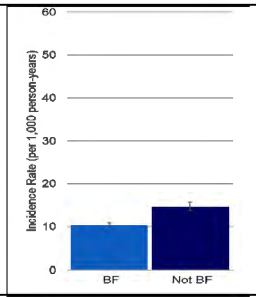
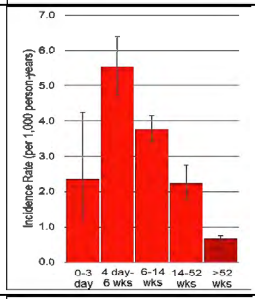
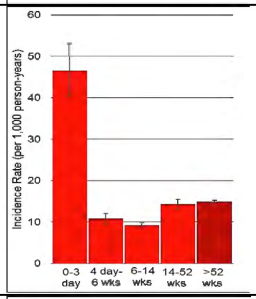
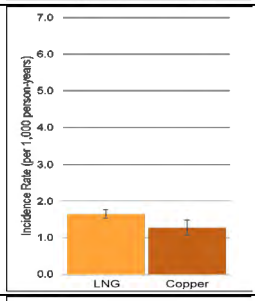
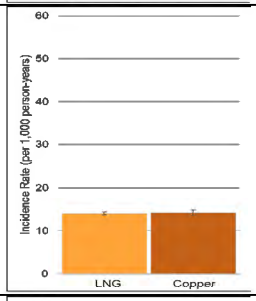
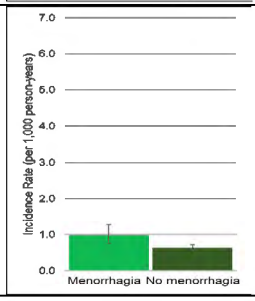
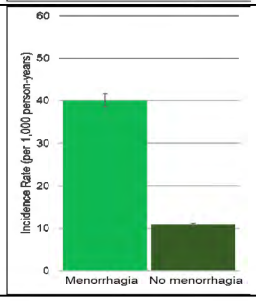
11.3 Interpretation

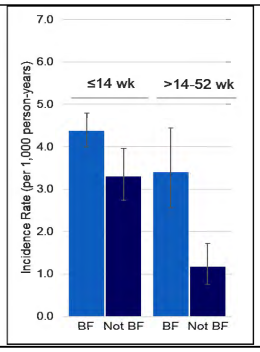
This study had a large, sociodemographically diverse population with rich data providing the opportunity to evaluate the risk of uterine perforation and IUD expulsion in the setting of usual clinical practice in the US. A total of 326,658 women with at least one IUD insertion were followed for a total of 641,427 person-years after their first insertion. In sum, 1,008 uterine perforations and 8,943 IUD expulsions were identified in the complete study population.

Overall, the incidence of uterine perforation was low, with an incidence rate of 1.6 per 1,000 person-years of follow-up in the complete study population and in the population with IUD type available. The incidence was higher (3.7 perforations per 1,000 person-years) in women with an IUD inserted within the first 52 weeks postpartum (the population in which breastfeeding information was available).

The incidence of IUD expulsion is about 10-fold higher than uterine perforation. In the complete study population, the incidence of IUD expulsion was 13.9 per 1,000 person-years of follow-up; for those with IUD type available, the incidence of IUD expulsion was 14.0 per 1,000 person-years. The incidence was slightly lower (11.6 expulsions per 1,000 person-years) in the group with an IUD inserted within the first 52 weeks postpartum with information on breastfeeding status. A summary of the magnitude and direction of the key objectives is in Table 60.

Table 60: Incidence rates and magnitude and direction of associations for risk of each outcome based on pooled adjusted hazard ratios

Exposure group vs. comparator	Uterine perforation		IUD expulsion	
	Crude incidence rate	Risk (adjusted HR)	Crude incidence rate	Risk (adjusted HR)
Breastfeeding vs. not breastfeeding among women ≤ 52 weeks postpartum		↑ 40%		↓ 30%
Early postpartum IUD insertion vs. > 52 weeks or no delivery		↑ 170% (0 to 3 days PP) ↑ 570% to 190% (4 days to 52 weeks PP)		↑ 430% (0 to 3 days PP) ↑ 6% to 40% (4 days to 52 weeks PP, no time trend)
LNG-IUDs vs. copper IUDs		↑ 50%		↓ 30%
Recent menorrhagia diagnosis (in previous 12 months) vs. no recent diagnosis, excluding women ≤ 52 weeks PP		↑ 50%		↑ 180%

Exposure group vs. comparator	Uterine perforation		IUD expulsion	
	Crude incidence rate	Risk (adjusted HR)	Crude incidence rate	Risk (adjusted HR)
Postpartum x breastfeeding		↑ 40% for early PP in BF grp ↑ 160% for early PP in not BF grp ↑ 30% for BF in early PP grp ↑ 140% for BF in later PP grp	Not applicable	Not applicable

BF = breastfeeding; HR = hazard ratio; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system, PP = postpartum.

Intrauterine devices are a generally effective and safe method of contraception. However, under conditions when the risk of uterine perforation is higher (earlier postpartum timing of IUD insertion, breastfeeding), providers should be aware of the risks so they can counsel their patients and perhaps consider timing and methods to reduce the risk of uterine perforation.

Similarly, under conditions where IUD expulsion rates are quite high (immediate postpartum IUD placement, menorrhagia), follow-up visits to ensure the IUD is in place should be done. In particular, women who have an IUD inserted immediately postpartum are at high risk of expulsion, and women diagnosed with menorrhagia in the previous 12 months are at high risk of expulsion. Therefore, to prevent unplanned pregnancies, women should be counseled about the elevated risk IUD expulsion and informed to look for signs of expulsion (e.g., no removal threads) and need for IUD replacement or alternate form of contraception in the event of an expulsion. Providers should be aware of elevated risks in the postpartum period and inform their patients of this risk, while considering higher comparative risks due to pregnancy without contraception.

11.4 Generalizability

This study included women enrolled in health care plans with electronic medical records in four regions of the US. The age, race, and ethnicity of the study population is quite diverse and is reflective of the population of the US with health insurance coverage. Three of the sites are located in western United States, and the fourth is in the midwest. Clinical practice differs in different regions of the country, but the results in this study are generally consistent across the sites.

12. Other information

This study was a PMR from the FDA and designed to evaluate the risk of uterine perforation and IUD expulsion in relation to postpartum timing of IUD insertion, breastfeeding at the time of IUD insertion, IUD type (LNG-releasing versus copper), and recent diagnosis of menorrhagia. There were no measures of effectiveness in this study, so benefits cannot be described in the context of this study.

13. Conclusion

Overall incidence of IUD-associated uterine perforation was low (ranging from 0.6 to 5.5 per 1,000 person-years depending on the exposure [e.g., postpartum timing, menorrhagia] and category of the

exposure [e.g., 4 days to ≤ 6 weeks, no menorrhagia]), and should be considered within the context of risks related to pregnancy in women who do not use contraception or less efficacious contraception than an IUD. Uterine perforation appears to be greatest for IUDs placed from 4 days to 6 weeks postpartum. Clinicians should be aware of this risk, and consideration should be given to delaying IUD insertion to a later postpartum time period. The results also suggest that IUD insertions done within the first 3 days after delivery are less likely to result in a uterine perforation than those done in later postpartum time periods (e.g., 4 days to 14 weeks postpartum) which also has clinical implications for optimal timing of insertions. Breastfeeding at the time of IUD placement among women within 52 weeks postpartum compared with those not breastfeeding at the time of IUD insertion is also associated with a higher risk of uterine perforation. When looking at breastfeeding status and postpartum timing of IUD insertion simultaneously (with a 14-week postpartum time cut point), the incidence of uterine perforation was highest in women who had their IUD inserted in the earlier postpartum period (≤ 14 weeks) and were breastfeeding and lowest in those with their IUDs placed in the later postpartum period (> 14 weeks or after no delivery) and were not breastfeeding. A diagnosis of menorrhagia in the 12 months before IUD placement compared with no recent menorrhagia diagnosis was associated with a higher risk of uterine perforation. LNG-IUDs compared with copper IUDs also appeared to be associated with higher risk of uterine perforation, but the fact that Mirena, the most commonly used LNG-IUD, is indicated for menorrhagia confers the potential for some residual confounding that should be further explored. In addition, we recognize the potential for detection bias that might affect the estimates for LNG-IUD for both perforation (length of follow-up) and expulsion (return of menstrual bleeding).

Overall incidence of IUD expulsion was higher than incidence of uterine perforation, but was also relatively low. If unrecognized, complete IUD expulsion could result in unplanned pregnancy. IUD expulsions were most frequent with immediate postpartum placement; such women should have follow-up in the postpartum period to assess for expulsion. IUD expulsion was also higher among women with a diagnosis of menorrhagia in the previous 12 months, and counseling should be tailored to this population. Breastfeeding at the time of IUD insertion was related to a lower risk of expulsion and might be explained by uterine quiescence due to hormones while breastfeeding. Also, LNG-IUDs were related to a lower risk of expulsion when accounting for other expulsion risk factors (e.g., menorrhagia). The present study might have overestimated risks related to partial IUD expulsions, as our definition of partial IUD expulsion was rather conservative and included malpositioned IUDs recognized on ultrasound that were replaced by the clinician.

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15. Appendices

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1a	Analysis tables	02 Mar 2020	List of Results Tables: Planned Analyses
1b	Analysis figures	02 Mar 2020	List of Results Figures: Planned Analyses
2	Post hoc analysis tables and figures	02 Mar 2020	List of Additional Results Tables and Figures: Post Hoc Analyses
3	Protocol	29 Jun 2018	Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUD Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)
4	Statistical analysis plan	24 Oct 2018	Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUD Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)
5	Operational definitions	26 Mar 2019	Operational Definitions with Data Structure Template
6	NLP definitions	07 Oct 2019	APEX IUD Natural Language Processing Terms and Algorithms for Defining Variables
7	Validation study report	08 Aug 2017	Validation Study on Uterine Perforation and Breast-feeding in Electronic Medical Record Databases

Annex 2. Signature pages

Signature Page – Study Responsible

Study Title:	Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUD Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)
Product:	Intrauterine contraceptives: Plastic IUD with progestogen (ATC code G02BA03) and Plastic IUD with copper (ATC code G02BA02); Mirena®, Skyla®, Liletta®, Kyleena®, and ParaGard® intrauterine devices
IMPACT Study Number:	19682
Study Type:	PASS
EU PAS Register Number:	33461
Development phase:	Post-Authorization
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I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

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Signature Page – Pharmacovigilance/ Benefit Risk Management

Study Title:	Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUD Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)
Product:	Intrauterine contraceptives: Plastic IUD with progestogen (ATC code G02BA03) and Plastic IUD with copper (ATC code G02BA02); Mirena®, Skyla®, Liletta®, Kyleena®, and ParaGard® intrauterine devices
IMPACT Study Number:	19682
Study Type:	PASS
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Product:	Intrauterine contraceptives: Plastic IUD with progestogen (ATC code G02BA03) and Plastic IUD with copper (ATC code G02BA02); Mirena®, Skyla®, Liletta®, Kyleena®, and ParaGard® intrauterine devices
IMPACT Study Number:	19682
Study Type:	PASS
EU PAS Register Number:	33461
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Signature Page – Medical Affairs

Study Title:	Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUD Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)
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Signature Page – Study Statistician- Medical Affairs Statistics

Study Title:	Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUD Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)
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IMPACT Study Number:	19682
Study Type:	PASS
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Signature Page – RTI Health Solutions, Coordinating Center Leader

Signature Page – RTI Health Solutions, Coordinating Center Leader

Study Title:	Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUD Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)
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IMPACT Study Number:	19682
Study Type:	PASS
EU PAS Register Number:	33461
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Study Title:	Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUD Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)
Product:	Intrauterine contraceptives: Plastic IUD with progestogen (ATC code G02BA03) and Plastic IUD with copper (ATC code G02BA02); Mirena®, Skyla®, Liletta®, Kyleena®, and ParaGard® intrauterine devices
IMPACT Study Number:	19682
Study Type:	PASS
EU PAS Register Number:	33461
Development phase:	Post-Authorization
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Signature Page – Regenstrief Institute – Data Source Research Partner Principal Investigator

Study Title:	Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUD Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)
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IMPACT Study Number:	19682
Study Type:	PASS
EU PAS Register Number:	33461
Development phase:	Post-Authorization
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Address:	Indianapolis, IN, 46202 USA

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Signature Page – KPSC – Data Source Research Partner Principal Investigator

Study Title:	Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUD Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)
Product:	Intrauterine contraceptives: Plastic IUD with progestogen (ATC code G02BA03) and Plastic IUD with copper (ATC code G02BA02); Mirena®, Skyla®, Liletta®, Kyleena®, and ParaGard® intrauterine devices
IMPACT Study Number:	19682
Study Type:	PASS
EU PAS Register Number:	33461
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Signature Page – RTI Health Solutions, Coordinating Center Statistician

Study Title:	Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUD Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)
Product:	Intrauterine contraceptives: Plastic IUD with progestogen (ATC code G02BA03) and Plastic IUD with copper (ATC code G02BA02); Mirena®, Skyla®, Liletta®, Kyleena®, and ParaGard® intrauterine devices
IMPACT Study Number:	19682
Study Type:	PASS
EU PAS Register Number:	33461
Development phase:	Post-Authorization
Sponsor's Name and Address:	Bayer AG, 13342 Berlin
Function:	RTI Health Solutions, Coordinating Center Statistician
Name:	PPD
Title:	
Address:	Research Triangle Park, NC, 27709 USA

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Date, Signature: 5 Mar 2020 PPD

Confidentiality statement:

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Signature Page – KPNC – Data Source Research Partner Principal Investigator

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Study Type:	PASS
EU PAS Register Number:	33461
Development phase:	Post-Authorization
Sponsor's Name and Address:	Bayer AG, 13342 Berlin
Function:	KPNC – Data Source Research Partner Principal Investigator
Name:	PPD
Title:	
Address:	Oakland, CA, 94612 USA

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Date, Signature: 03/09/2020 PPD

Confidentiality statement: PPD

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