Demographic, Reproductive, and Medical Risk Factors for Intrauterine Device Expulsion

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OBJECTIVE: To explore to what extent intrauterine device (IUD) expulsion is associated with demographic and clinical risk factors.

METHODS: The APEX-IUD (Association of Perforation and Expulsion of IntraUterine Devices) study was a U.S. cohort study using electronic health records from three integrated health care systems (Kaiser Permanente Northern California, Southern California, and Washington) and a health care information exchange (Regenstrief Institute). These analyses included individuals aged 50 years or younger with IUD insertions from 2001 to 2018. Intrauterine device expulsion cumulative incidence and incidence rates were estimated. Using Cox regression models, hazard ratios with 95% CIs were estimated before and after adjustment for risk factors of interest (age, race and ethnicity, parity, body mass index [BMI], heavy menstrual bleeding, and dysmenorrhea) and potential confounders.

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RESULTS: In total, 228,834 individuals with IUD insertion and no delivery in the previous 52 weeks were identified (184,733 [80.7%] with levonorgestrel-releasing intrauterine system). Diagnosis of heavy menstrual bleeding—particularly a diagnosis in both recent and past periods—was the strongest risk factor for IUD expulsion. Categories with the highest risk of IUD expulsion within each risk factor included individuals diagnosed with overweight, obesity, and morbid obesity; those in younger age groups, especially among those aged 24 years or younger; and in those with parity of four or more. Non-Hispanic White individuals had the lowest incidence and risk, and after adjustment, Asian or Pacific Islander individuals had the highest risk. Dysmenorrhea was not independently associated with expulsion risk when adjusting for heavy menstrual bleeding.

CONCLUSION: Most risk factors for expulsion identified in this study appear consistent with known physiologic factors that affect uterine anatomy and physiology (age, BMI, heavy menstrual bleeding, parity). The increased risk of IUD expulsion among individuals of color warrants further investigation. Intrauterine devices are an effective long-term contraceptive; expulsion is uncommon, but patients should be counseled accordingly.

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Although APEX-IUD was conducted to address a postmarketing requirement from the U.S. Food and Drug Administration, data from the study were also used to address questions raised by the European Medicines Agency about specific demographic, reproductive, and medical risk factors associated with IUD expulsion. The objective of this analysis of APEX-IUD data was to determine the extent to which six variables of interest to the European Medicines Agency were independent risk factors for IUD expulsion among individuals with no record of delivery in the past year—age, race and ethnicity, parity, BMI, history of heavy menstrual bleeding, and history of dysmenorrhea—and the extent to which these risk factor associations differed for LNG-IUD compared with copper IUD users.

METHODS

APEX-IUD was a retrospective cohort study using data from electronic health records (EHRs), conducted within three integrated health care systems (Kaiser Permanente Northern California, Kaiser Permanente Southern California, and Kaiser Permanente Washington) and a research site using data from a health care information exchange in Indiana (Regenstrief Institute). The study design and validation of variable selection have been described in detail previously. Approval or exemption for the conduct of this study was provided by the IRBs of Kaiser Permanente Northern California, Kaiser Permanente Southern California, Kaiser Permanente Washington, and Regenstrief Institute; Kaiser Permanente Southern California also received approval from California state agencies for the use of vital statistics data.

The APEX-IUD study population included individuals aged 50 years or younger at the time of IUD insertion and in the health care system for 12 months or longer before IUD insertion; only the first IUD insertion in the study period was included. To reduce the effects of confounding by breastfeeding or early postpartum timing at IUD insertion,4,12,16,18 and the effect of pregnancy on BMI measurement, these analyses excluded individuals with a delivery 52 weeks or less before IUD insertion. Individuals were followed from IUD insertion until IUD expulsion, uterine perforation, removal, reinsertion, or expiration (ie, end of the approved duration of use); pregnancy; hysterec-
tomy or other sterilization procedure; death; disenrollment from the health care system; or end of the study period (June 30, 2018).

Categories for the risk factors of interest at the time of IUD insertion, including age, race and ethnicity (self-reported and as identified in the...
Box 1. Risk Factors

Age category (y)
- 20 or younger
- 21–24
- 25–28
- 29–32
- 33–36
- 37–50 (ref)

Race and ethnicity
- Asian or Pacific Islander
- Hispanic Black or Hispanic other
- Hispanic White
- Non-Hispanic Black
- Non-Hispanic White (ref)
- None of the above or multiple
- Unknown

Parity
- 0 (ref)
- 1
- 2
- 3
- 4 or more
- Missing

BMI category
- Underweight (lower than 18.5)
- Normal weight (18.5–24.9) (ref)
- Overweight (25.0–29.2)
- Obesity (30.0–39.9)
- Morbid obesity (40.0 or higher)
- Missing

HMB diagnosis
- In recent and past periods
- Only recent (1 y or less before index only)
- Only past (more than 1 y before index only)
- No diagnosis (ref)

Dysmenorrhea diagnosis
- In recent and past periods
- Only recent (1 y or less before index only)
- Only past (more than 1 y before index only)
- No diagnosis (ref)

Ref, reference; BMI, body mass index; HMB, heavy menstrual bleeding.
Definitions for these variables are described in detail in Anthony et al.16

EHR), parity, BMI measurement closest to IUD insertion, history of heavy menstrual bleeding, and history of dysmenorrhea, are shown in Box 1.

The outcome of interest, IUD expulsion, was determined from the EHR, including clinical notes, using algorithms developed and validated for this purpose.17 Both complete expulsions (defined as an IUD located in the vagina, not present in the uterus or abdomen on imaging, or with documented reports that the IUD was expelled or “fell out”) and partial expulsions (defined as visualization of the IUD extruding from the external cervical os or present in the cervix on imaging) were included. An IUD malpositioned in the uterine cavity (eg, imaging demonstrated the IUD in the lower uterine segment but not the cervix) was considered an expulsion only if removed by the clinician.

Baseline demographics and clinical characteristics at IUD insertion were analyzed descriptively. Crude incidence rates for each risk factor category were calculated as the number of expulsions occurring during the time at risk divided by the total person-years at risk. Crude incidence rates are reported as the number of expulsions per 1,000 person-years with exact 95% CIs calculated based on the relationship between the Poisson distribution and the chi-square distribution as described by Dobson et al.19 Crude cumulative incidence, defined as the proportion of IUD insertions in which expulsion occurred over time, was estimated for each risk factor using the Kaplan-Meier method. Incidence rates and cumulative incidence were further stratified by IUD type for each risk category.

Hazard ratios (HRs) and 95% CIs from Cox regression models evaluated associations of the risk factors with IUD expulsion. Crude HRs were estimated from separate models, each including one risk factor. The adjusted hazard ratios (aHRs) were estimated from a single model that included all risk factors, plus the following additional covariates for adjustment of potential confounding effects that were selected based on their association with IUD expulsion: research site, IUD type, calendar year of the index date, leiomyoma diagnosis, concomitant gynecologic procedures, indicator of difficult insertion, and annualized number of IUD insertions performed by the health care professional in the previous year.16 Hazard ratios of IUD expulsion were estimated for each category relative to the reference category for that variable (Box 1); missing data were included as a separate category. To further assess the extent to which the association of covariates with IUD expulsion varied by IUD type, adjusted Cox models were conducted separately for LNG-IUD and copper IUD insertions.

RESULTS

The analysis cohort included 228,834 individuals (LNG-IUD: 184,733 [80.7%]; copper IUD: 41,123 [18.0%]; unknown IUD type: 2,978 [1.3%]) (Fig. 1). The maximum follow-up time was 10 years, and the
average length of follow-up was 2.0 years. Compared with copper IUD users, LNG-IUD users had a higher mean age (33.4±9.1 vs 31.8±8.2 years), a lower proportion of nulliparous individuals (26.2% vs 31.5%), and a higher mean BMI (28.7±7.5 vs 26.9±6.2) (Table 1). Any prior heavy menstrual bleeding diagnosis (recent, past, or both) was more common among LNG-IUD users (21.2%) than copper IUD users (4.8%), as was any prior dysmenorrhea diagnosis (12.6% vs 6.0%).

There were 6,762 expulsions in the complete cohort, yielding a crude incidence rate of 14.9 per 1,000 person-years (95% CI 14.6–15.3) [data not shown]. For each risk factor evaluated, Table 2 and Appendix 1 present the crude incidence rate of IUD expulsion; Table 3 and Appendix 2 present the cumulative incidence of IUD expulsion (Appendices 1 and 2 are available online at http://links.lww.com/AOG/C926). For all risk factor categories, the cumulative incidence of IUD expulsion at 5 years was approximately double the incidence at 1 year, suggesting that about half of expulsions occurred in the first year.

Crude incidence rates and cumulative incidence of IUD expulsion were highest in individuals in the oldest (37–50 years) and two youngest (20 years or younger and 21–24 years) age categories (Tables 2 and 3). Incidence rates in the other age categories were intermediate and similar to each other. Compared with the oldest age group, all younger groups had lower IUD expulsion risk in the crude analysis (Fig. 2). After adjustment, all younger age groups had a higher risk of IUD expulsion than the comparator group, with the highest risk in the youngest age group (20 years or younger) and a trend toward lower aHRs with increasing age.

Crude incidence rate and cumulative incidence of IUD expulsion were highest among non-Hispanic Black individuals and lowest among non-Hispanic White individuals (Tables 2 and 3). Compared with non-Hispanic White individuals, all other groups had a higher crude risk of IUD expulsion (Fig. 2). After adjustment, the aHRs were generally attenuated, but all groups continued to have higher risks than the comparator group.

Crude incidence rate and cumulative incidence of IUD expulsion were highest in those with parity of four or more and lowest in those with parity of two (Tables 2 and 3). In the crude analysis, those with parity of four or more had the highest risk of IUD expulsion, those with parity of three had lower but still increased risk, and those with parity of one or two was not substantially different from the comparator group (0 parity) (Fig. 2). After adjustment, the group with parity of four or more still showed a higher risk of IUD expulsion, those with parity of two had a 10% lower risk of IUD expulsion, and those with parity of one or three had a risk similar to that of the comparator group.

The crude incidence rate of IUD expulsion was similar in the underweight and normal-weight BMI categories and then increased across increasing BMI categories (Table 2). The cumulative incidence of
Table 1. Characteristics of the Analysis Population*

| Variable | Complete Cohort | LNG-IUD Cohort | Copper IUD Cohort |
|----------|----------------|----------------|------------------|
| No. of individuals | 228,834 | 184,733 | 41,123 |
| Person-years at risk | 453,004 | 366,321 | 81,434 |
| Age (y) | 33.1±8.9 | 33.4±9.1 | 31.8±8.2 |
| 20 or younger | 20,440 (8.9) | 16,717 (9.0) | 3,433 (8.3) |
| 21–24 | 28,021 (12.2) | 21,614 (11.7) | 6,303 (14.6) |
| 25–28 | 29,031 (12.7) | 22,396 (12.1) | 6,051 (15.0) |
| 29–32 | 30,099 (13.2) | 23,259 (12.6) | 6,835 (15.5) |
| 33–36 | 31,969 (14.0) | 25,354 (13.7) | 6,226 (15.1) |
| 37–50† | 89,274 (39.0) | 75,393 (40.8) | 12,868 (31.3) |
| Race and ethnicity | | | |
| Asian or Pacific Islander | 26,344 (11.5) | 20,398 (11.0) | 5,677 (13.8) |
| Hispanic Black or Hispanic other‡ | 41,226 (18.0) | 33,039 (17.9) | 8,017 (19.5) |
| Hispanic White | 22,150 (9.7) | 17,600 (9.5) | 4,403 (10.7) |
| Non-Hispanic Black | 20,727 (9.1) | 17,626 (9.5) | 2,820 (6.9) |
| Non-Hispanic White† | 101,546 (44.4) | 82,820 (44.8) | 16,904 (41.1) |
| None of the above or multiple | 11,514 (5.0) | 9,194 (5.0) | 2,229 (5.4) |
| Unknown or missing | 5,327 (2.3) | 4,056 (2.2) | 1,069 (2.6) |
| Parity§ | | | |
| 0† | 61,915 (27.1) | 48,395 (26.2) | 12,959 (31.5) |
| 1 | 34,382 (15.0) | 28,085 (15.2) | 6,129 (14.9) |
| 2 | 55,053 (24.1) | 45,119 (24.4) | 9,716 (23.6) |
| 3 | 24,822 (10.8) | 20,753 (11.2) | 3,980 (9.7) |
| 4 or more | 10,759 (4.7) | 9,169 (5.0) | 1,553 (3.8) |
| Missing | 41,903 (18.3) | 33,212 (18.0) | 6,708 (16.5) |
| BMI (kg/m²) | 28.4±7.3 | 28.7±7.5 | 26.9±6.2 |
| Underweight (lower than 18.5) | 3,123 (1.4) | 2,370 (1.3) | 717 (1.7) |
| Normal weight (18.5–24.9)† | 84,291 (36.8) | 65,451 (35.4) | 17,911 (43.6) |
| Overweight (25.0–29.9) | 62,693 (27.4) | 50,142 (27.1) | 11,444 (28.8) |
| Obesity (30.0–39.9) | 56,501 (24.7) | 47,357 (25.6) | 8,452 (20.6) |
| Morbid obesity (40 or higher) | 17,232 (7.5) | 15,298 (8.3) | 1,659 (4.0) |
| Missing | 4,994 (2.2) | 4,115 (2.2) | 540 (1.3) |
| HMB diagnosis | | | |
| Recent (12 mo or less before index only) | 22,610 (9.9) | 21,708 (11.8) | 620 (1.5) |
| In recent and past periods | 8,990 (3.9) | 8,747 (4.7) | 108 (0.3) |
| Past (more than 1 y before index only) | 10,135 (4.4) | 8,706 (4.7) | 1,244 (3.0) |
| No diagnosis† | 187,099 (81.8) | 145,572 (78.8) | 39,151 (95.2) |
| Dysmenorrhea diagnosis | | | |
| Recent (12 mo or less before index only) | 9,101 (4.0) | 8,356 (4.5) | 588 (1.4) |
| In recent and past periods | 3,838 (1.7) | 3,585 (1.9) | 185 (0.4) |
| Past (more than 1 y before index only) | 13,207 (5.8) | 11,251 (6.1) | 1,575 (4.1) |
| No diagnosis† | 202,688 (88.6) | 161,541 (87.4) | 38,077 (94.0) |
| Leiomyomas | 13,736 (6.0) | 12,738 (6.9) | 774 (1.9) |
| Concomitant gynecologic procedure† | 24,545 (10.7) | 21,726 (11.8) | 2,375 (5.8) |
| Any difficult IUD insertion‡ | 26,797 (11.7) | 22,298 (12.1) | 4,076 (9.9) |
| Health care professional annualized no. of insertions in previous year‡ | 42.0 [28.0, 60.0] | 39.0 [23.0, 56.0] | 42.0 [27.3, 60.0] |
| Missing | 18,932 | 13,684 | 2,090 |
| Calendar year of IUD insertion | | | |
| 2001–2009 | 9,702 (4.2) | 7,209 (3.9) | 1,965 (4.8) |
| 2010 | 19,985 (8.7) | 15,533 (8.4) | 4,190 (10.2) |
| 2011 | 21,102 (9.2) | 16,836 (9.1) | 3,964 (9.6) |
| 2012 | 24,343 (10.6) | 19,618 (10.6) | 4,469 (10.9) |
| 2013 | 23,934 (10.5) | 19,551 (10.6) | 4,230 (10.3) |
| 2014 | 24,110 (10.5) | 19,782 (10.7) | 4,171 (10.1) |
| 2015 | 27,222 (11.9) | 22,076 (12.0) | 4,822 (11.7) |

(continued)
Table 1. Characteristics of the Analysis Population* (continued)

| Variable               | Complete Cohort | LNG-IUD Cohort | Copper IUD Cohort |
|------------------------|-----------------|----------------|------------------|
|                        | 2016            | 2017           | 2018             |
|                        | 31,052 (13.6)   | 25,367 (13.7)  | 5,131 (12.9)     |
|                        | 35,437 (15.5)   | 29,034 (15.7)  | 5,961 (14.5)     |
|                        | 11,947 (5.2)    | 9,727 (5.3)    | 2,038 (5.0)      |

LNG-IUD, levonorgestrel-releasing intrauterine system; IUD, intrauterine device; BMI, body mass index; HMB, heavy menstrual bleeding. Data are mean±SD, n (%), or median (quartile 1, quartile 3) unless otherwise specified.

* The analysis population included individuals with no delivery in the 52 weeks before the first observed IUD insertion.

† Reference category for each risk factor.

‡ The cohort included a high proportion of individuals of Hispanic other ethnicity because most individuals in the Kaiser Permanente Northern California system with Hispanic ethnicity had unknown race.

§ Defined as the number of pregnancies reaching a gestational age of 20 weeks or more. For some insertions, parity was determined as nonzero but the exact count was uncertain; for these insertions, parity was coded as missing.

¶ At least one of the following: abortion, aspiration and curettage, dilation and curettage, excision or biopsy of cervix or uterus, ablation, colposcopy and other cervical procedures, hysteroscopy procedure, laminaria procedure, laparoscopy, lysis adhesions, myomectomy, nerve procedure, salpingectomy, or oophorectomy. Although abortion was included in the list of concomitant procedures, the timing of IUD insertions relative to the date of abortion was not collected.

§ At least one of the following: cervical dilation, ultrasound guidance, paracervical block, difficult insertion noted, use of misoprostol.

* Available only in Kaiser Permanente Northern California, Kaiser Permanente Southern California, and Kaiser Permanente Washington; for Regenstrief Institute, this was coded as missing.

IUD expulsion increased with higher BMI overall (Table 3). In the crude analyses of risk, risk of IUD expulsion increased with higher BMI (Fig. 2). After adjustment, the aHRs were slightly attenuated, but the pattern of increasing risk of IUD expulsion with higher BMI remained.

The crude incidence rate and cumulative incidence of IUD expulsion were highest in individuals with an heavy menstrual bleeding diagnosis in both recent and past periods (Tables 2 and 3). Compared with no heavy menstrual bleeding diagnosis, individuals with both recent and past heavy menstrual bleeding diagnoses had the highest crude risk of IUD expulsion, individuals with only a recent diagnosis had a lower but still elevated risk, and individuals with only a past diagnosis had an even lower elevated risk (Fig. 2). After adjustment, the aHRs for IUD expulsion were attenuated but still higher than for the comparator group.

The crude incidence rate and cumulative incidence of IUD expulsion were highest in individuals with a dysmenorrhea diagnosis in both recent and past periods, and both were similar to those of individuals with only a recent diagnosis of dysmenorrhea (Tables 2 and 3). In the crude analysis of risk, individuals with any dysmenorrhea diagnosis had an elevated risk of expulsion relative to no diagnosis (Fig. 2). After adjustment, the aHRs were attenuated, and none of the groups with a dysmenorrhea diagnosis in the recent period, past period, or both had a risk of IUD expulsion that was different from the comparator.

Comparing aHRs by IUD type (copper vs LNG-IUD), different patterns were seen than were observed in the overall analysis for age, race and ethnicity, and parity (Fig. 3). Younger age was more strongly associated with a higher risk of IUD expulsion among copper IUD users than LNG-IUD users. Among LNG-IUD users, Asian or Pacific Islander, Hispanic Black or Hispanic other, Hispanic White, and non-Hispanic Black races and ethnicities were more strongly associated with a higher risk of expulsion than non-Hispanic White; among copper IUD users, Asian or Pacific Islander and Hispanic White individuals had a marginally higher risk of expulsion than non-Hispanic White individuals. Having one or more previous births appeared to be associated with a lower risk of IUD expulsion compared with those with 0 parity in copper IUD users. For LNG-IUD users, four or more previous births were associated with an increased expulsion risk, whereas one–three previous births were not associated with an increased or decreased risk of expulsion. For BMI, the pattern of risk of expulsion was highest in individuals with morbid obesity (compared with normal weight) and was consistent in both LNG-IUD and copper IUD users; however, the risk for the overweight and obesity groups was substantially attenuated in copper compared with LNG-IUD users. For heavy menstrual bleeding, the aHR was highest for those with both recent and past heavy menstrual bleeding for both copper and LNG-IUD users; however, the risk for those with only recent or only past heavy menstrual bleeding was attenuated for copper IUDs. Dysmenorrhea was not associated with increased risk of expulsion for either IUD type after adjustments were made for other exposures and covariates.
DISCUSSION

Among individuals with no delivery in the year before IUD insertion (after mutual adjustment for all other risk factors and covariates), heavy menstrual bleeding diagnosis—particularly a diagnosis in both recent and past periods—was the strongest risk factor for IUD expulsion, in terms of both absolute incidence and magnitude of risk (HR and aHR). Intrauterine device expulsion incidence and risk were also elevated in individuals diagnosed as having overweight, obesity, and...
## Table 3. Crude Cumulative Incidence of Intrauterine Device Expulsion at 1 Year and 5 Years Among Levonorgestrel-Releasing and Copper Intrauterine Device Insertions

| Risk Factor and Category | Complete Cohort | LNG-IUD Cohort | Copper IUD Cohort |
|--------------------------|----------------|----------------|------------------|
|                          | 1y             | 5y             | 1y               |
| **Age (y)**              |                |                |                  |
| 20 or younger            | 2.43 (2.21–2.67) | 5.01 (4.49–5.58) | 1.87 (1.66–2.10) |
| 21–24                    | 2.12 (1.94–2.31) | 4.69 (4.12–5.34) | 1.64 (1.47–1.84) |
| 25–28                    | 1.71 (1.55–1.89) | 3.45 (3.07–3.87) | 1.48 (1.31–1.67) |
| 29–32                    | 2.02 (1.85–2.20) | 4.36 (3.97–4.78) | 1.95 (1.76–2.16) |
| 33–36                    | 2.06 (1.90–2.24) | 4.45 (4.11–4.82) | 2.17 (1.98–2.37) |
| 37–50                    | 3.15 (3.02–3.27) | 5.62 (5.42–5.83) | 3.47 (3.33–3.61) |
| **Race and ethnicity**   |                |                |                  |
| Asian or Pacific Islander| 3.21 (2.98–3.45) | 6.07 (5.66–6.52) | 3.36 (3.10–3.64) |
| Hispanic Black or Hispanic other | 3.14 (2.96–3.33) | 6.01 (5.66–6.39) | 3.31 (3.10–3.53) |
| Hispanic White           | 2.67 (2.45–2.91) | 4.51 (4.14–4.91) | 2.94 (2.68–3.23) |
| Non-Hispanic Black       | 3.84 (3.56–4.14) | 7.27 (6.75–7.83) | 4.13 (3.82–4.47) |
| Non-Hispanic White       | 1.79 (1.71–1.89) | 3.72 (3.54–3.91) | 1.64 (1.54–1.73) |
| None of the above or multiple | 2.38 (2.09–2.70) | 5.43 (4.79–6.15) | 2.51 (2.19–2.89) |
| **Parity**               |                |                |                  |
| 0                        | 2.37 (2.24–2.50) | 4.88 (4.56–5.22) | 2.05 (1.91–2.19) |
| 1                        | 2.52 (2.35–2.71) | 5.09 (4.73–5.47) | 2.56 (2.36–2.77) |
| 2                        | 2.43 (2.30–2.58) | 4.67 (4.43–4.92) | 2.66 (2.50–2.82) |
| 3                        | 3.12 (2.89–3.37) | 5.59 (5.21–6.00) | 3.46 (3.20–3.74) |
| 4 or more                | 4.71 (4.29–5.17) | 7.71 (7.06–8.41) | 5.21 (4.74–5.74) |
| Missing                  | 1.74 (1.61–1.89) | 3.90 (3.57–4.25) | 1.60 (1.46–1.75) |
| **BMI (kg/m²)**          |                |                |                  |
| Underweight (lower than 18.5) | 1.94 (1.47–2.56) | 3.29 (2.46–3.49) | 1.34 (0.92–1.96) |
| Normal weight (18.5–24.9) | 1.78 (1.69–1.88) | 3.64 (3.44–3.85) | 1.58 (1.48–1.69) |
| Overweight (25.0–29.9)   | 2.39 (2.26–2.52) | 4.55 (4.31–4.81) | 2.42 (2.28–2.57) |
| Obesity (30.0–39.9)      | 3.32 (3.16–3.49) | 6.14 (5.85–6.44) | 3.52 (3.34–3.71) |
| Morbid obesity (40 or higher) | 4.23 (3.91–4.57) | 8.81 (8.18–9.48) | 4.46 (4.12–4.83) |
| **HMB diagnosis**        |                |                |                  |
| In recent and past periods | 8.37 (7.76–9.02) | 13.96 (12.96–15.03) | 8.51 (7.89–9.18) |
| Recent only (1 y or less before index date only) | 6.46 (6.11–6.82) | 11.27 (10.70–11.87) | 6.62 (6.26–6.99) |
| Past only (more than 1 y before index date only) | 3.03 (2.67–3.43) | 5.54 (4.88–6.29) | 3.01 (2.64–3.44) |
| No diagnosis             | 1.71 (1.64–1.77) | 3.59 (3.46–3.73) | 1.53 (1.46–1.60) |
| **Dysmenorrhea diagnosis** | 4.11 (3.47–4.88) | 8.18 (6.69–9.98) | 4.23 (3.56–5.04) |
| In recent and past periods | 4.49 (4.04–4.99) | 7.58 (6.80–8.45) | 4.60 (4.12–5.13) |
| Recent only (1 y or less before index date only) | 3.03 (2.72–3.38) | 5.80 (5.09–6.61) | 3.09 (2.75–3.47) |
| Past only (more than 1 y before index date only) | 2.34 (2.27–2.42) | 4.67 (4.52–4.81) | 2.35 (2.27–2.43) |

(continued)
morbid obesity; in younger age groups, especially those aged 24 years or younger; and in those with parity of four or more. Non-Hispanic White individuals had the lowest incidence and risk, and after adjustment, Asian or Pacific Islander individuals had the highest risk. Individuals of non-Hispanic Black, Hispanic Black and Hispanic other, Hispanic White, and none of the above or multiple race or ethnicity had an adjusted risk of expulsion that was higher than non-Hispanic White individuals, but lower than Asian or Pacific Islander individuals. After adjustment for other risk factors and covariates, dysmenorrhea was not associated with a higher risk of IUD expulsion.

Our finding that diagnosed heavy menstrual bleeding is a risk factor for IUD expulsion is consistent with other APEX-IUD analyses and with other studies. One of the LNG-IUD types has an indication for treatment of heavy menstrual bleeding, and the majority of individuals with a recent or past diagnosis of heavy menstrual bleeding, or both, were LNG-IUD users in our study. An increased risk of expulsion in individuals with a history of heavy menstrual bleeding was also observed in the (much smaller) copper IUD cohort. Individuals with increased BMI are at higher risk for irregular periods and heavy menstrual bleeding, but we saw only modest attenuation of the HRs for BMI or heavy menstrual bleeding when adjusting for other risk factors and potential confounders.

Body mass index also emerged as an important risk factor for IUD expulsion, and the relationship of increasing rate of IUD expulsion with higher BMI (higher than 25) is consistent with the literature. Increased inflammation

Table 3. Crude Cumulative Incidence of Intrauterine Device Expulsion at 1 Year and 5 Years Among Levonorgestrel-Releasing and Copper Intrauterine Device Insertions (continued)

| Risk Factor and Category | LNG-IUD Cohort | Copper IUD Cohort |
|--------------------------|----------------|-------------------|
|                         | 5 y            | 1 y               | 5 y               |
| Non-Hispanic White       | 3.34 (3.15–3.54) | 2.62 (2.36–2.90) | 5.66 (5.09–6.30) |
| None of the above or multiple | 5.53 (4.82–6.35) | 1.91 (1.37–2.64) | 5.13 (3.77–6.96) |
| Parity†                  |                |                   |
| 0                        | 4.07 (3.75–4.42) | 3.60 (3.26–3.98) | 8.03 (7.14–9.04) |
| 1                        | 5.24 (4.85–5.67) | 2.34 (1.95–2.80) | 4.30 (3.56–5.20) |
| 2                        | 4.89 (4.63–5.17) | 1.41 (1.18–1.68) | 3.64 (3.11–4.27) |
| 3                        | 6.10 (5.67–6.56) | 1.37 (1.03–1.82) | 2.79 (2.23–3.37) |
| 4 or more                | 8.28 (7.57–9.06) | 1.65 (1.09–2.50) | 4.30 (3.01–6.12) |
| Missing                  | 3.47 (3.13–3.85) | 2.65 (2.25–3.11) | 6.46 (5.45–7.65) |
| BMI (kg/m²)‡             |                |                   |
| Underweight (lower than 18.5) | 2.65 (1.76–3.97) | 4.11 (2.73–6.16) | 5.70 (3.89–8.31) |
| Normal weight (18.5–24.9) | 3.19 (2.99–3.42) | 2.56 (2.31–2.82) | 5.43 (4.91–6.01) |
| Overweight (25.0–29.9)   | 4.52 (4.25–4.80) | 2.30 (2.03–2.62) | 4.84 (4.24–5.51) |
| Obesity (30.0–39.9)      | 6.34 (6.02–6.67) | 2.25 (1.92–2.63) | 5.14 (4.41–5.98) |
| Morbid obesity (40 or higher) | 8.89 (8.24–9.59) | 2.38 (1.70–3.33) | 7.96 (5.81–10.84) |
| HMB diagnosis            |                |                   |
| In recent and past periods | 14.12 (13.10–15.21) | 4.43 (1.67–11.48) | 11.32 (5.27–23.41) |
| Recent only (1 y or less before index date only) | 11.39 (10.81–12.00) | 2.42 (1.41–4.15) | 7.85 (5.10–11.78) |
| Past only (more than 1 y before index date only) | 5.30 (4.63–6.08) | 3.48 (2.48–4.86) | 7.47 (5.15–10.78) |
| No diagnosis             | 3.22 (3.08–3.37) | 2.39 (2.22–2.56) | 5.16 (4.80–5.53) |
| Dysmenorrhea diagnosis   |                |                   |
| In recent and past periods | 8.04 (6.58–9.92) | 2.61 (0.99–6.81) | 14.04 (5.05–35.68) |
| Recent only (1 y or less before index date only) | 7.63 (6.83–8.52) | 3.03 (1.83–5.02) | 7.06 (3.98–12.39) |
| Past only (more than 1 y before index date only) | 5.41 (4.72–6.19) | 2.90 (2.10–4.00) | 9.33 (6.22–13.86) |
| No diagnosis             | 4.59 (4.43–4.75) | 2.39 (2.23–2.57) | 5.12 (4.77–5.49) |

LNG-IUD, levonorgestrel-releasing intrauterine system; IUD, intrauterine device; BMI, body mass index; HMB, heavy menstrual bleeding. Data are % (95% CI).

* Percentage of insertions with unknown race and ethnicity: all: 2.3%; LNG-IUD: 2.2%; copper IUD: 2.6%.
† Percentage of insertions with missing parity: all: 18.3%; LNG-IUD: 18.0%; copper IUD: 16.5%.
‡ Percentage of insertions with missing BMI category: all: 2.2%; LNG-IUD: 2.2%; copper IUD: 1.3%.
Fig. 2. Pooled crude and adjusted hazard ratios of intrauterine device (IUD) expulsion. Adjusted hazard ratios (HRs) were estimated from a Cox model including body mass index (BMI), menorrhagia diagnosis, age, parity, race and ethnicity, dysmenorrhea diagnosis, site, IUD type, calendar year of index date, leiomyomas, any concomitant gynecologic procedures, any indicator of difficult insertion, and annualized number of IUD insertions performed by a health care professional in the previous year. Percentage of insertions missing BMI category: 2.2%; percentage of insertions missing parity: 18.3%; percentage of insertions with unknown race and ethnicity: 2.3%. Hispanic other included individuals who indicated Hispanic ethnicity and either selected “other” for race or did not select a race at all. HMB, heavy menstrual bleeding.

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| Age category (vs. 37-50 years) | Crude hazard ratio (95% CI) | Adjusted hazard ratio (95% CI) |
|---------------------------------|----------------------------|-------------------------------|
| ≤20 years                       | 0.85 (0.78-0.93)           | 1.76 (1.58-1.95)              |
| 21-24 years                     | 0.73 (0.67-0.79)           | 1.46 (1.32-1.61)              |
| 25-28 years                     | 0.59 (0.54-0.65)           | 1.13 (1.02-1.25)              |
| 29-32 years                     | 0.70 (0.65-0.76)           | 1.19 (1.09-1.30)              |
| 33-36 years                     | 0.73 (0.68-0.79)           | 1.06 (0.98-1.15)              |

| Race/ethnicity (vs. non-Hispanic White) | Crude hazard ratio (95% CI) | Adjusted hazard ratio (95% CI) |
|-----------------------------------------|----------------------------|-------------------------------|
| Asian/Pacific Islander                 | 1.72 (1.59-1.85)           | 1.80 (1.66-1.94)              |
| Hispanic Black or Hispanic other       | 1.69 (1.58-1.81)           | 1.40 (1.31-1.50)              |
| Hispanic White                         | 1.36 (1.25-1.48)           | 1.25 (1.14-1.38)              |
| Non-Hispanic Black                     | 2.07 (1.92-2.24)           | 1.49 (1.38-1.62)              |
| None of the above or multiple          | 1.43 (1.28-1.60)           | 1.27 (1.13-1.42)              |

| Parity (vs. 0)                        | Crude hazard ratio (95% CI) | Adjusted hazard ratio (95% CI) |
|---------------------------------------|----------------------------|-------------------------------|
| 1                                     | 1.05 (0.97-1.14)           | 0.97 (0.89-1.05)              |
| 2                                     | 0.99 (0.93-1.06)           | 0.90 (0.84-0.98)              |
| 3                                     | 1.21 (1.12-1.31)           | 0.97 (0.88-1.06)              |
| ≥4                                    | 1.77 (1.61-1.95)           | 1.26 (1.13-1.40)              |

| BMI (vs. normal weight)               | Crude hazard ratio (95% CI) | Adjusted hazard ratio (95% CI) |
|---------------------------------------|----------------------------|-------------------------------|
| Underweight                           | 1.00 (0.78-1.28)           | 0.98 (0.76-1.26)              |
| Overweight                            | 1.29 (1.21-1.38)           | 1.20 (1.13-1.29)              |
| Obesity                               | 1.77 (1.67-1.89)           | 1.55 (1.45-1.66)              |
| Morbid obesity                        | 2.49 (2.30-2.70)           | 2.02 (1.86-2.20)              |

| HMB (vs. no diagnosis of HMB)         | Crude hazard ratio (95% CI) | Adjusted hazard ratio (95% CI) |
|---------------------------------------|----------------------------|-------------------------------|
| Diagnosis of HMB in recent and past periods | 4.67 (4.33-5.03) | 3.81 (3.49-4.17) |
| Recent diagnosis of HMB                | 3.52 (3.33-3.73)           | 3.20 (2.99-3.42)              |
| Past diagnosis of HMB                  | 1.70 (1.52-1.91)           | 1.63 (1.45-1.83)              |

| Dysmenorrhea (vs. no diagnosis of dysmenorrhea) | Crude hazard ratio (95% CI) | Adjusted hazard ratio (95% CI) |
|------------------------------------------------|----------------------------|-------------------------------|
| Diagnosis of dysmenorrhea in recent and past periods | 1.76 (1.51-2.05) | 1.02 (0.88-1.20) |
| Recent diagnosis of dysmenorrhea             | 1.79 (1.62-1.97)           | 1.04 (0.94-1.15)              |
| Past diagnosis of dysmenorrhea               | 1.27 (1.15-1.40)           | 1.04 (0.94-1.15)              |
Fig. 3. Crude and adjusted hazard ratios of intrauterine device (IUD) expulsion by IUD type. For each IUD type, adjusted hazard ratios (HRs) were estimated from a Cox model including body mass index (BMI), menorrhagia diagnosis, age, parity, race and ethnicity, dysmenorrhea diagnosis, site, calendar year of index date, leiomyomas, any concomitant gynecologic procedures, any indicator of difficult insertion, and annualized number of IUD insertions performed by a health care professional in the previous year. Percentage of insertions missing BMI category, levonorgestrel-releasing intrauterine system (LNG-IUD): 2.2%; copper IUD: 1.3%; percentage of insertions missing parity, LNG-IUD: 18.0%; copper IUD: 16.5%; percentage of insertions with unknown race and ethnicity: LNG-IUD, 2.2%; copper IUD, 2.6%. Hispanic other included individuals who indicated Hispanic ethnicity and either selected “other” for race or did not select a race at all. HMB, heavy menstrual bleeding.

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associated with greater adiposity has been proposed as a mechanism for higher expulsion risk (Saito-Tom L et al. Obstet Gynecol 2017;129:66S–7S. doi: 10.1097/AOG.0000514850.20849.1f). Also, it is possibly more challenging to place the IUD at the fundus due to body habitus in individuals with obesity, which could lead to a higher risk of expulsion. We adjusted for difficult insertion; however, our variable may not have been adequately sensitive to capture nuanced difficulties with insertion.

Race and ethnicity are social constructs, rather than rooted in biological differences, and our findings should be interpreted with caution. Rates of IUD expulsion were higher in all other race and ethnicity groups than in non-Hispanic White individuals, specifically among those with LNG-IUDs, even after adjusting for other risk factors and covariates. Racial and ethnic differences in diagnosed risk factors for expulsion may be a partial explanation for the more pronounced expulsion risk differences by race and ethnicity in the LNG-IUD group, but equally likely are the existence of cultural constructs not in our data.

Younger age groups had a lower risk of IUD expulsion in our crude analyses, consistent with prior evidence, but had a higher risk of IUD expulsion after adjustment, suggesting that age may be largely confounded by other factors. The risk of expulsion among younger age groups appears to be a stronger predictor for individuals with copper IUDs than among those with LNG-IUDs, as previous studies have found. One might hypothesize that younger nulliparous individuals would have a higher risk of IUD expulsion due to smaller uterine cavity and more challenging IUD placement due to nulliparity.

This study has several strengths, including a large and demographically diverse population. The evidence from this study reflects routine clinical practice in the United States; thus, the potential for selection and recall biases is minimal. Finally, the analytic approach enabled the evaluation of each risk factor independently, with adjustment for other risk factors plus additional covariates.

This study has limitations. The date of IUD expulsion reflects the date it came to medical attention, not necessarily the exact date of the expulsion. Risk factors may differ for partial compared with complete expulsions, which were not differentiated in the analysis (both were included). It is possible that some malpositioned IUDs were removed because of the individual’s choice and not because of the position of the IUD, but, because this was conducted as a safety study, we chose to err on the side of overcounting expulsions rather than undercounting. A comparatively small number of individuals had copper IUDs, decreasing the precision of the estimates. Although data were missing for 2% of most variables, 18.3% of the cohort had missing data for parity, and some misclassification in parity could have occurred if individuals had a delivery outside the health care systems not captured in clinical notes. The results for the parity variable should be interpreted in light of the greater proportion (18%) of data that was missing for that variable. Heavy menstrual bleeding and dysmenorrhea were based on diagnosis codes but were not validated clinically, nor was severity captured. Although a diagnosis of uterine leiomyomas was included in the multivariable models to control for confounding, underlying uterine pathology may have been present but unrecorded in some cases. We did not control for other conditions associated with increased uterine inflammation and uterine contractions, such as adenomyosis. Finally, the results reflect IUD use in U.S. clinical practice (eg, to manage heavy menstrual bleeding) and may not be generalizable to other populations.

In conclusion, of the six factors evaluated in this study, the risk of IUD expulsion was highest among individuals with a diagnosis of heavy menstrual bleeding, particularly in both the recent and past periods. Higher BMI; younger age at IUD insertion; four or more previous births; and non-Hispanic Black, Hispanic Black, Hispanic White, Asian or Pacific Islander, and multiple racial and ethnic groups (compared with non-Hispanic White) were all associated with a higher risk of IUD expulsion when accounting for other potential confounders. Dysmenorrhea was not associated with an elevated risk of IUD expulsion after adjustment. The risk of IUD expulsion among individuals with heavy menstrual bleeding should not deter clinicians from continuing their practice of treatment of severe heavy menstrual bleeding with an LNG-IUD. Intrauterine devices are an effective long-term contraceptive method, and IUD expulsion is uncommon. Most risk factors for IUD expulsion identified by our study appear consistent with known physiologic factors affecting uterine anatomy and physiology (age, BMI, heavy menstrual bleeding, parity). The increased risk of IUD expulsion among individuals of color warrants further investigation. Clinicians should counsel individuals with characteristics that might put them at higher risk of IUD expulsion about signs of complete or partial IUD expulsion, potential risk of pregnancy, and what to do if they suspect their IUD has been expelled.
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RTI Health Solutions led the design of the study, analysis, reporting, and interpretation of the results in collaboration with study team members from Kaiser Permanente Northern California, Kaiser Permanente Southern California, Kaiser Permanente Washington, Regenstrief Institute, and Bayer. Kaiser Permanente Northern California, Kaiser Permanente Southern California, Kaiser Permanente Washington, and Regenstrief Institute extracted the data, reviewed and confirmed a portion of the outcomes, compiled the datasets, and transferred the data to RTI Health Solutions. All co-authors had access to aggregated data and participated in the development of the protocol, statistical analysis plan, and study report. The contracts between Bayer AG and each of the other organizations [Kaiser Permanente Northern California, Kaiser Permanente Southern California, Kaiser Permanente Washington, Regenstrief Institute, RTI Health Solutions] include independent publication rights. Bayer AG was provided the opportunity to review the manuscript prior to submission and comments were advisory only.

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