Association Between Intrauterine Device Type and Risk of Perforation and Device Expulsion: Results From the APEX-IUD Study

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Condensation: Uterine perforation risk is low overall and modestly greater with levonorgestrel-releasing versus copper intrauterine devices; risk of expulsion is modestly lower with levonorgestrel-releasing intrauterine devices.

Short title: Incidence and risk of uterine perforation and expulsion by IUD type

Key Words: intrauterine device, IUD, expulsion, uterine perforation, levonorgestrel IUD, copper IUD, electronic health records, natural language processing, algorithm, data linkage, free text, propensity score overlap weighting

91 # AJOG AT A GLANCE

92 **A. Why was this study conducted?**

93 It is important to understand how intrauterine device type (levonorgestrel-releasing or copper) is
94 associated with the risk of uterine perforation and device expulsion in United States clinical
95 practice.

96 **B. What are the key findings?**

97 Rates of uterine perforations and device expulsions were low n both users of levonorgestrel and
98 copper devices, but perforation risk was approximately 50% higher for women using
99 levonorgestrel devices compared with copper devices. The risk of device expulsion was 30%
100 lower for women using levonorgestrel devices compared with copper devices.

101 **C. What does this study add to what is already known?**

102 In light of low absolute rates of uterine perforation and expulsion, differences in risk by device
103 type may not be clinically significant.

STRUCTURED ABSTRACT

Background: Intrauterine devices, including levonorgestrel-releasing and copper devices, are highly effective long-acting reversible contraceptives. Potential risks associated with intrauterine devices are low and include uterine perforation and device expulsion.

Objective: To evaluate the risk of perforation and expulsion associated with levonorgestrel-releasing devices versus copper in clinical practice in the United States

Study design: APEX-IUD was a retrospective cohort study of women aged ≤50 years with an intrauterine device insertion during 2001-2018, and information on intrauterine device type, as well as patient and medical characteristics. Four research sites with access to electronic health records contributed data for the study: three Kaiser Permanente integrated healthcare systems (Northern California, Southern California and Washington) and one using data from a healthcare information exchange in Indiana (Regenstrief Institute). Perforation was classified as any extension of the device into or through the myometrium. Expulsion was classified as complete (not visible in uterus or abdomen or patient-reported) or partial (any portion in cervix or malpositioned). We estimated, by intrauterine device type, crude incidence rates and crude cumulative incidence. Perforation and expulsion risk comparing levonorgestrel devices to copper was estimated using Cox proportional hazards regression with propensity score overlap weighting to adjust for confounders.

Results: Among the 322,898 women included in this analysis, the incidence (95% confidence interval) of perforation per 1,000 person-years was 1.64 (1.53-1.76) for levonorgestrel devices and 1.27 (1.08-1.48) for copper devices; cumulative 1-year and 5-year crude incidence (95% confidence interval), respectively, was 0.22% (0.20%-0.24%) and 0.63% (0.57%-0.68%) for

levonorgestrel devices and 0.16% (0.13%-0.20%) and 0.55% (0.44%-0.68%) for copper devices. The incidence (95% confidence interval) of expulsion per 1,000 person-years was 13.95 (13.63-14.28) for levonorgestrel devices and 14.08 (13.44-14.75) for copper devices; cumulative 1-year and 5-year crude incidence (95% confidence interval), respectively, was 2.30% (2.24%-2.36%) and 4.52% (4.40%-4.65%) for levonorgestrel devices and 2.30% (2.18%-2.44%) and 4.82% (4.56%-5.10%) for copper devices. Adjusted hazard ratios (95% confidence intervals) were 1.49 (1.25-1.78) for perforation and 0.69 (0.65-0.73) for expulsion comparing levonorgestrel to copper devices.

Conclusions: After adjusting for potential confounders, levonorgestrel devices were associated with an increased risk of uterine perforation and a decreased risk of expulsion relative to copper devices. Given that the absolute numbers of these events are low in both groups, these differences may not be clinically meaningful

138 # INTRODUCTION

139 An estimated 14% of women worldwide use intrauterine devices (IUDs).[1] IUDs provide highly
140 effective contraception, with rates of unintended pregnancy of less than 1%.[2] Two types of IUDs
141 are widely used: levonorgestrel (LNG) releasing IUDs, which are approved by the United States
142 (US) Food and Drug Administration (FDA) for use up to 3 to 6 years; and copper IUDs,
143 approved for use up to 10 years before removal or replacement.[3-7]

144 Risks associated with IUD use are rare and include uterine perforation and IUD expulsion. The
145 prospective observational European Active Surveillance Study for Intrauterine Devices
146 (EURAS-IUD) evaluated the incidence and risk of uterine perforation by IUD type, finding a
147 borderline higher risk of perforation among users of LNG-IUDs compared with copper IUDs.[8,9]
148 Earlier analyses of expulsion rate by IUD type have yielded varied findings. In the Contraceptive
149 CHOICE study, the 36-month cumulative expulsion rate did not differ by IUD type,[10] whereas a
150 meta-analysis evaluating rates of IUD expulsion by IUD type found a greater rate of expulsion
151 with LNG-IUDs than with copper IUDs after vaginal delivery.[11]

152 We conducted a multi-site US cohort study, Association of Perforation and EXpulsion of
153 IntraUterine Devices (APEX-IUD), to evaluate risk factors associated with IUD-related uterine
154 perforations and IUD expulsion as observed in clinical practice.[12] Associations between
155 postpartum timing of IUD insertion and breastfeeding with uterine perforation and IUD
156 expulsion have been reported previously (Reed et al., *Lancet*, in press; Armstrong et al., *JAMA*
157 *Network Open*, in press). Here, we compare the incidence and risk of uterine perforation and
158 expulsion associated with LNG-IUDs versus copper IUDs. At the time of the study, four brands
159 of LNG-IUDs (Mirena [Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ], Liletta

160 [Allergan USA, Inc., Irvine, CA; Medicines360, San Francisco, CA], Skyla [Bayer HealthCare
161 Pharmaceuticals Inc., Whippany, NJ], and Kyleena [Bayer HealthCare Pharmaceuticals Inc.,
162 Whippany, NJ]) and one copper IUD (ParaGard [CooperSurgical, Inc., Trumbull, CT]) were
163 approved for use in the US.

164 MATERIALS AND METHODS

165 Four research sites contributed data for the study: three integrated healthcare systems Kaiser
166 Permanente Northern California (KPNC), Kaiser Permanente Southern California (KPSC), and
167 Kaiser Permanente Washington (KPWA)—and one using data from a healthcare information
168 exchange in Indiana Regenstrief Institute (RI). The study methods, as well as the validation of
169 algorithms to identify uterine perforation and IUD expulsion and confirm availability of
170 breastfeeding status at time of IUD insertion have been described in detail previously.[12,13]

171 Study Cohort

172 The APEX-IUD population included 326,658 women aged ≤50 years at the time of IUD
173 insertion between 2001 and 2018. Women were required to have at least 12 months of
174 enrollment in the healthcare plans or to have had a clinical encounter within the health
175 information exchange more than 12 months prior to IUD insertion. Of this population, 322,898
176 women had information on IUD type recorded in their electronic health record (EHR) and were
177 included in the present analysis (Figure 1). The first date for inclusion in the study was the
178 beginning of 2001 for RI, 2007 for KPWA, 2009 for KPSC, and 2010 for KPNC; the last date
179 for inclusion at all research study sites was April 30, 2018. Only data for a woman's first IUD
180 insertion in the study period were included in this analysis. All participating research study sites

181 received approval or exemption for the conduct of this study by their respective institutional
182 review boards. KPSC also received approval from the California Health and Human
183 Services Agency and the California Department of Public Health Center for Health Statistics
184 and Informatics for the use of vital statistics.

185 **Exposure and Covariates**

186 Variables were ascertained retrospectively from the research sites' data systems using a mixture
187 of structured data (National Drug Codes, International Classification of Diseases, Ninth
188 Revision/Tenth Revision, Clinical Modification [ICD-9-CM/10-CM], Healthcare Common
189 Procedure Coding System [HCPCS], and Current Procedural Terminology [CPT] codes) and
190 unstructured data (clinical notes via natural language processing [NLP]). The primary exposure
191 of interest, IUD type, was identified via drug, procedural, or diagnostic codes and NLP.

192 The date of IUD insertion was used as the index date. For the outcome evaluations, person-time
193 at risk was calculated from the IUD insertion date until the first occurrence of a study outcome
194 (uterine perforation or IUD expulsion) or censoring event. Censoring events included IUD
195 expiration (based on FDA-approved duration of use for the IUD brand, plus 3 months to allow
196 for the normal variability in clinical visits for removal or replacement of IUDs), removal, or
197 reinsertion; pregnancy, hysterectomy, bilateral oophorectomy, or other sterilization procedure;
198 disenrollment from the healthcare system (for the KP sites) or date of last clinical encounter in
199 the healthcare system (for RI); death; or end of the study period (June 30, 2018). For RI, the last
200 clinical encounter before December 1, 2018 was considered the most recent.

201 Covariates at index date included research site, demographics (age and race/ethnicity),
202 postpartum status (nonpostpartum [i.e., nulliparous or >52 weeks postpartum] or postpartum

203 timing of insertion [for women <52 weeks postpartum]), breastfeeding status, clinical
204 characteristics, procedure- and provider-related characteristics, and other potential risk factors at
205 the time of IUD insertion based on all available information during the look-back period, which
206 extended to the earliest enrollment date (KP sites) or clinical encounter (RI). Risk factors
207 included smoking status during the past 12 months, body mass index (BMI, kg/m^2), reproductive
208 history, gynecologic diagnoses (e.g., dysmenorrhea, uterine fibroids), and information about the
209 IUD insertion procedure (year, indicators of difficult insertion).[12] Nonpostpartum women were
210 assumed not to be breastfeeding at IUD insertion. Breastfeeding status was classified as yes (last
211 breastfeeding date ≤ 30 days before IUD insertion or any time after IUD insertion, up to
212 12 months after delivery), no (documentation of not breastfeeding at or before insertion, or
213 breastfeeding data were missing at insertion and the most recent documentation of breastfeeding
214 [yes] was >30 days before insertion), or undetermined.

215 **Outcomes**

216 The outcomes of interest for this analysis were any IUD-related uterine perforation and any IUD
217 expulsion. Uterine perforation could be complete (i.e., clinical evidence of IUD in the pelvis or
218 abdominal cavity) or partial (i.e., IUD removed after being visualized as partially embedded in
219 the myometrium on imaging or hysteroscopy, or partial perforation noted by clinician at time of
220 removal). IUD expulsion could be complete (i.e., IUD located in the vagina, not present in the
221 uterus or abdomen on imaging, or patient reported that the IUD was expelled or "fell out") or
222 partial (i.e., any portion of IUD in the cervix on imaging, IUD extending through the cervix on
223 examination, or IUD considered malpositioned on imaging and removed by the clinician). These
224 outcomes were previously validated at each study site.[13] Chart abstraction and/or clinical note
225 review was performed to validate EHR-based algorithms or confirm perforations.[12]

Statistical Analysis

Descriptive analyses for all covariates were stratified by IUD type. For categorical variables, frequencies and percentages were calculated for each level. For continuous variables, mean, standard deviation, minimum, maximum, median, and quartiles were calculated. Missing data were treated as missing, and no imputations were performed. The variables BMI and parity included a "missing" category for analyses.

Crude incidence rates were calculated as the number of IUD-related uterine perforations and IUD expulsions occurring during the person-time at risk divided by the total person-time at risk (in person-years) and were reported as point estimates (number of cases per 1,000 person-years) with 95% confidence intervals (CIs). Crude cumu ative incidence, the number of IUD-related uterine perforations and IUD expulsions occurring up to a time point of the total number of IUD insertions, was estimated using the Kaplan Meier method.

Cox proportional hazards regression models were used to estimate crude hazard ratios (HRs) and are reported as point estimates with 95% CIs. The first 5 years of person-time at risk were considered in the HR analyses. Adjusted HRs were estimated using a Cox model with propensity score overlap weighting.[14] Propensity score models were developed separately for uterine perforation and IUD expulsion. Covariates were assessed for inclusion in propensity score models based on association with the study outcome if the crude HR was greater than 1.11 or less than 0.90; additional confounders were included if they yielded a ≥10% change in effect estimate of IUD type. Details for the propensity score models and the overlap weights have been described previously and are presented in Supplemental Appendix A.[12] The following variables were included in the propensity score models for adjustment for both perforation and expulsion

248 outcomes: postpartum status (4 categories), breastfeeding status, menorrhagia diagnosis in the
249 last 12 months, age (tertiles), race/ethnicity, calendar year of index date (categorical), BMI
250 (categorical), dysmenorrhea, uterine fibroids, parity (0, > 0, or missing), cesarean delivery at any
251 time before index date, live birth for the most recent delivery, concomitant gynecologic
252 procedure, indicator of difficult IUD insertion, provider experience (quartiles of IUD insertions
253 performed in past year), and research site. For the propensity score model for perforation,
254 additional variables included recent smoking, duration of look-back period (quartiles), and
255 cesarean delivery for most recent delivery. To further adjust for postpartum categories after a
256 lack of balance in initial propensity score models, an interaction of postpartum timing (4
257 categories) by site was added for the expulsion outcome.

258 To assess balance between IUD-type groups, absolute standardized differences were calculated
259 before and after weighting.[15] Groups were considered balanced if the standardized difference
260 was less than 0.20 (generally considered small).[16]

261 All analyses were performed using SAS software, version 9.3 or higher (SAS Institute, Inc.,
262 Cary, North Carolina).

263 **Role of the Funding Source**

264 Authors affiliated with the study sponsor (4 of 27) participated in designing the study;
265 interpretating the data; writing the report; and deciding to submit the paper for publication.

266 # RESULTS

267 ## Cohort Characteristics

268 The cohort for this analysis included 322,898 women: 259,234 (80.3%) women with LNG-IUDs
269 and 63,664 (19.7%) women with copper IUDs. Median duration of continuous enrollment
270 following IUD insertion was 2.4 years (range, 0-16.7 years).

271 The average age of copper IUD users was slightly lower than LNG-IUD users (31.2 years vs.
272 32.2 years), with a lower proportion of users aged 37 years or older (24.6% vs. 31.9%) (Table 1).
273 Proportionally fewer LNG-IUD than copper IUD users were breastfeeding at IUD insertion
274 (18.7% vs. 24.1%), and proportionally fewer were postpartum (28.7% vs. 35.4%). Proportionally
275 more LNG-IUD than copper IUD users had a BMI indicating obesity (34.4% vs. 27.2%) and had
276 a diagnosis of menorrhagia in the 12 months before IUD insertion (12.1% vs. 1.3%) (Table 1).
277 Proportionally more LNG-IUD than copper IUD users had a diagnosis of dysmenorrhea in the
278 year before IUD insertion (3.8% vs 1.6%) and had a history of uterine fibroids before IUD
279 insertion (6.0% vs. 2.5%) After propensity score weighting, all variables included in the
280 analyses of uterine perforation and IUD expulsion had satisfactory balance (absolute
281 standardized difference < 0.2) (data not shown).

282 ## Uterine Perforation

283 There were 996 IUD-related uterine perforations: 834 among 259,234 LNG-IUD insertions and
284 162 among 63,664 copper IUD insertions (Table 2). Among uterine perforations in LNG-IUD
285 users, 467 (56.0%) were complete, 363 (43.5%) were partial, and 4 (0.5%) were of an
286 undetermined type. Among uterine perforations in copper IUD users, 43 (26.5%) were complete
287 and 119 (73.5%) were partial. The crude incidence rate and cumulative crude incidence of

288 uterine perforation at 1 year and 5 years were somewhat higher among those with LNG-IUDs
289 versus copper IUDs (Table 2; Figure 2A). The crude incidence rate per 1,000 person-years was
290 1.64 (95% CI, 1.53-1.76) for LNG-IUDs and 1.27 (95% CI, 1.08-1.48) for copper IUDs. Crude
291 cumulative 1-year incidence for LNG-IUDs and copper IUDs was 0.22% (95% CI, 0.20%-
292 0.24%) and 0.16% (95% CI, 0.13%-0.20%), respectively; 5-year crude cumulative incidence for
293 LNG-IUDs and copper IUDs was 0.63% (95% CI, 0.57%-0.68%) and 0.55% (95% CI, 0.44%-
294 0.68%), respectively. The number of uterine perforations diagnosed for LNG-IUDs increased
295 more sharply approximately 5 years after IUD insertion (Figure 2A), which likely reflects the
296 uterine perforations that were recognized at the time the woman returned to have the IUD
297 removed or replaced. This trend was less obvious around the 10-year expiration for copper IUDs,
298 because the sample size dropped substantially after 5 years of follow-up.

299 Compared with women with copper IUDs those with LNG-IUDs were at a higher risk for
300 uterine perforation, with a crude HR of 1.34 (95% CI, 1.13-1.60) (Figure 3A). Propensity score
301 adjustment did not attenuate the point estimate: the adjusted HR was 1.49 (95% CI, 1.25-1.78).

302 **IUD Expulsion**

303 There were 8,872 IUD expulsions: 7,075 among 259,234 LNG-IUD insertions and 1,797 among
304 63,664 copper IUD insertions (Table 2). The crude incidence rate and cumulative crude
305 incidence for IUD expulsion at 1 year and 5 years were similar among those with LNG-IUDs and
306 copper IUDs (Table 2; Figure 2B). The crude incidence rate per 1,000 person-years was 13.95
307 (95% CI, 13.63-14.28) for LNG-IUDs and 14.08 (95% CI, 13.44-14.75) for copper IUDs. The
308 crude cumulative 1-year incidence for LNG-IUDs and copper IUDs was 2.30% (95% CI, 2.24%-
309 2.36%) and 2.30% (95% CI, 2.18%-2.44%), respectively; 5-year crude cumulative incidence for

310 LNG-IUDs and copper IUDs was 4.52% (95% CI, 4.40%-4.65%) and 4.82% (95% CI, 4.56%-
311 5.10%), respectively. There was an increase in the number of LNG-IUD expulsions
312 approximately 5 years after IUD insertion (Figure 2B), which likely reflects the IUD expulsions
313 that were recognized at the time the woman returned to have the IUD removed or replaced. This
314 trend is not seen near the 10-year expiration for copper IUDs because only two sites had the
315 potential for 10 years of follow-up, and the sample size dropped rapidly after 5 years of follow-
316 up.

317 Compared with women with copper IUDs, those with LNG-IUDs were at a marginally lower risk
318 for IUD expulsion, with a crude HR of 0.96 (95% CI, 0.91-1.01) before adjustment (Figure 3B).
319 After propensity score adjustment, the lower risk was more pronounced (adjusted HR, 0.69;
320 95% CI, 0.65-0.73).

321 We also evaluated the extent to which IUD type (LNG-IUD vs. copper IUD) modified the
322 association between IUD expulsion and postpartum timing of IUD insertion for women with
323 IUD insertion at different time periods postpartum: ≤ 6 weeks, > 6 and ≤ 14 weeks, > 14 and ≤
324 52 weeks versus IUD insertion more than 52 weeks postpartum (including no recorded delivery
325 within the past 52 weeks) (see Supplemental Appendix B). When compared with women with
326 IUD insertion > 52 weeks postpartum or no delivery (referent), women with IUD insertion > 6 to
327 ≤ 14 weeks postpartum had a lower or similar risk of IUD expulsion, while women with IUD
328 insertion ≤ 6 weeks or > 14 to ≤ 52 weeks postpartum had a similar or higher risk, for both LNG-
329 IUD and copper IUD users.

330 ## DISCUSSION

331 We observed that incidences of uterine perforation and of device expulsion differed modestly for
332 users of levonorgestrel and copper devices. After adjusting for potential confounders, users of
333 levonorgestrel devices were at increased risk of uterine perforation (adjusted HR, 1.49) and a
334 decreased risk of expulsion (adjusted HR, 0.69) relative to users of copper devices.

335 The crude cumulative incidence of uterine perforation at 1 year was 0 22% for those receiving
336 LNG-IUDs and 0.16% for those receiving copper IUDs; at 5 years, the crude cumulative
337 incidence was 0.63% for LNG-IUDs and 0.55% for copper IUDs. These results are similar to
338 those from EURAS-IUD, which also found a small absolute difference in perforation rates
339 between IUD types and an elevated risk of uterine perforation with LNG-IUDs versus copper
340 (50% in APEX-IUD and 60% in EURAS IUD).[8] The crude incidence of uterine perforation over
341 1 year of follow-up in EURAS-IUD was 1.4 per 1,000 insertions among those receiving
342 LNG-IUDs and 1.1 per 1,000 insertions for copper IUDs.[8] EURAS-IUD followed 39,009 of the
343 original study population of 61,448 women for up to 5 years and reported a perforation incidence
344 of 2.1 per 1,000 insertions in the LNG-IUD group and 1.6 per 1,000 insertions in the copper IUD
345 group (adjusted odds ratio, 1.7; 95% CI, 1.0-2.8).[9]

346 In our study, the crude incidence and cumulative incidence of IUD expulsions at 1 and 5 years
347 were relatively similar between those with an LNG-IUD and those with a copper IUD. The most
348 commonly used LNG-IUDs have an indication for menorrhagia, which is a known risk factor for
349 IUD expulsion; adjusting for menorrhagia in the propensity scores would reduce the impact of
350 confounding due to different proportion of women with menorrhagia among copper and LNG-
351 IUD users.

352 Findings from prior analyses of expulsion rate by IUD type have yielded inconsistent findings. In
353 a secondary analysis of the Contraceptive CHOICE study (N = 5,403), no meaningful differences
354 in 36-month cumulative expulsion rate per 100 users were observed by IUD type (10.1 for 4,219
355 LNG-IUD users vs. 10.7 for 1,184 copper IUD users; $P = 0.99$).[10] Differences in findings from
356 the Contraceptive CHOICE study and APEX-IUD may be due to population differences,
357 particularly with respect to age (three-quarters of women in the Contraceptive CHOICE analysis
358 were aged 14 to 29 years, whereas roughly one-third of women in our analysis were younger
359 than 29 years) and parity (40% of women in Contraceptive CHOICE were nulliparous vs.
360 approximately 20% in our analysis). Further, whereas APEX-IUD evaluated EHR for expulsion
361 outcomes, in Contraceptive CHOICE most data on expulsions were reported by patients and,
362 thus, the ability to detect partial expulsions was limited. Finally, we noted an increase in
363 expulsions at 5 years, when women visited their provider for removal or replacement of LNG-
364 IUDs, while the 3-year follow-up period for Contraceptive CHOICE ended during the approved
365 duration of use for LNG-IUDs.[10]

366 In addition, a meta-analysis evaluating rates of IUD expulsion by postpartum timing of insertion
367 and IUD type found that, among postpartum women with IUD insertion immediately (<10
368 minutes) after vaginal delivery, those using LNG-IUDs had a greater risk of expulsion compared
369 with those using copper IUDs (adjusted risk ratio, 1.90; 95% CI, 1.36-2.65).[11] For IUD types
370 placed during cesarean delivery, the point estimate for LNG-IUDs was lower than for copper
371 IUDs, but the CI included a null effect (adjusted risk ratio, 0.52; 95% CI, 0.22-1.22). In our
372 study, users of LNG-IUDs and copper IUDs inserted > 6 to ≤ 14 weeks postpartum had a lower
373 or similar risk of IUD expulsion, while women with IUD insertion ≤ 6 weeks or > 14 to

374 ≤ 52 weeks postpartum had a similar or higher risk, compared with women with IUD insertion
375 > 52 weeks postpartum or no delivery.

376 Clinical Implications

377 Despite statistically significant findings, results of these analyses do not suggest clinically
378 significant differences in the risk of IUD-related uterine perforation or IUD expulsion with
379 LNG-IUDs versus copper IUDs. Additional research is needed to explore the health outcomes
380 and women's subjective experience of uterine perforation and IUD expulsion.

381 Strengths and Limitations

382 A key strength of the study is its size (larger than any prior report) with a long duration of data
383 available (median 2.4 years following IUD insertion) and demographically diverse cohort. The
384 outcome measures were previously validated in each data source.[13] The databases used in this
385 study contain detailed covariates with at least 12 months' look-back from clinical and health
386 claims records that allowed robust propensity score development and adjusting for the
387 confounding by indication anticipated and observed in the LNG-IUD insertions.

388 Nonetheless, some limitations are acknowledged. Although the analyses were adjusted for
389 multiple confounders, the potential for residual confounding due to unmeasured factors remains.
390 While the duration of use of copper IUDs (up to 10 years) was beyond the duration of follow-up
391 at two of the sites, the analyses of cumulative incidence and HRs included only the time for
392 which there was data for both types. Even so, this might have led to an overestimation of
393 outcomes for LNG-IUDs because proportionally more LNG-IUD users than copper IUD users
394 would have had a return for an IUD removal or replacement recorded in their EHR during the
395 study period, owing to the shorter window to expiration for LNG-IUDs, although only 10% of

396 the patients with copper IUD remained at risk after 5 years. In contrast, women using a copper
397 IUD were more likely to be censored upon leaving the system before their IUD expiration.
398 Potential differences in outcomes between specific IUD brands may be of interest, owing to
399 differences in approved duration of use and prescribing patterns; however, the analyses were
400 stratified only by IUD type (LNG vs. copper) and did not differentiate among IUD brands. While
401 proportionally more complete perforations were observed for LNG-IUD users (56.0% of
402 perforations) than for copper IUD users (26.5% of perforations), our incidence and risk analyses
403 did not distinguish between complete perforations (which may require laparoscopy or
404 laparotomy) and partial perforations (which can typically be treated with a minor procedure
405 during a clinic or outpatient surgery visit) or between complete and partial expulsions.
406 Differences in the risk of complete versus partial perforation by IUD type may be a direction for
407 future research. For the purposes of this safety study, we erred on the side of being more
408 inclusive in our outcome definitions, which may have resulted in overestimation of a small
409 proportion of partial perforations and of some expulsions wherein the devices were only partially
410 expelled. Although not all sites classified IUD expulsions as complete or partial, rates of
411 complete and partial expulsions among the 5,471 expulsions further classified in the full study
412 cohort of 326,658 women have been reported previously: 2,616 (47.8%) were complete, 2,480
413 (45.3%) were partial, and 375 (6.9%) were of an undetermined type (Armstrong et al., *JAMA*
414 *Network Open*, in press).

415 CONCLUSION

416 The cumulative incidence of IUD-related uterine perforation was higher for users of LNG-IUDs
417 than for users of copper IUDs but was low for both groups. The cumulative incidence of IUD

418 expulsion was comparable for users of LNG-IUDs and copper IUDs. After adjusting for potential
419 confounders, users of LNG-IUDs were at increased risk of uterine perforation and a decreased
420 risk of IUD expulsion relative to users of copper IUDs.

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426

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481

482 # TABLES

483 **Table 1. Characteristics of the APEX-IUD US Study Cohort, by IUD Type, 2001-**

484 **2018**

Characteristics	IUD Type: LNG-IUD (N = 259,234)	IUD Type: Copper IUD (N = 63,664)	Unweighted Absolute Standardized Differences[a]
Person-years at risk	507,151.2	127,587.0	
Age, mean (SD), years	32.2 (8.5)	31.2 (7.4)	0.121
Age categories, n (%)			
≤28 years	94,007 (36.3)	23,929 (37.6)	0.027
29-36 years	82,637 (31.9)	24,083 (37.8)	0.125
37-50 years	82,590 (31 9)	15,652 (24.6)	0.162
Race/ethnicity, n (%)			
Asian/Pacific Islander	29,574 (11.4)	8,995 (14.1)	0.082
Hispanic Black	572 (0.2)	117 (0.2)	0.008
Hispanic Other	44,261 (17.1)	11,705 (18.4)	0.034
Hispanic White	32,736 (12.6)	9,543 (15.0)	0.068
Non-Hispanic Black	23,750 (9.2)	4,211 (6.6)	0.095
Non-Hispanic White	110,479 (42.6)	24,423 (38.4)	0.087
Other or multiple	12,862 (5.0)	3,367 (5.3)	0.015
Unknown	5,000 (1.9)	1,303 (2.0)	0.008
Body mass index (kg/m^2), n (%)			
Underweight	2,807 (1.1)	845 (1.3)	0.022
Normal weight	87,499 (33.8)	25,045 (39.3)	0.116
Overweight	75,421 (29.1)	19,817 (31.1)	0.044
Obese	89,069 (34.4)	17,344 (27.2)	0.155
Missing	4,438 (1.7)	613 (1.0)	0.065
Breastfeeding status, n (%)			
Yes	48,447 (18.7)	15,330 (24.1)	0.132

Characteristics	IUD Type		Unweighted Absolute Standardized Differences[a]
	LNG-IUD (N = 259,234)	Copper IUD (N = 63,664)	
No	23,754 (9.2)	6,674 (10.5)	0.044
Undetermined/No delivery in the past year	187,033 (72.1)	41,660 (65.4)	0.145
Recent smoker, n (%)	26,502 (10.2)	5,559 (8.7)	0.051
Postpartum status, n (%)			
≤ 6 weeks	15,631 (6.0)	4,228 (6.6)	0.025
> 6 to ≤ 14 weeks	42,760 (16.5)	12,934 (20 3)	0.099
> 14 to ≤ 52 weeks	16,110 (6.2)	5,379 (8 4)	0.086
Nonpostpartum (> 52 weeks or no delivery)	184,733 (71.3)	41,123 (64.6)	0.143
Parity, n (%)			
0	48,399 (18.7)	12,960 (20.4)	0.043
> 0	180 134 (69.5)	44,247 (69.5)	0.000
Missing	30,701 (11.8)	6,457 (10.1)	0.054
Menorrhagia in 12 months before IUD insertion, n (%)	31,291 (12.1)	834 (1.3)	0.441
Dysmenorrhea diagnosis in 12 months before IUD insertion, n (%)	9,724 (3.8)	995 (1.6)	0.136
History of uterine fibroids before IUD insertion, n (%)	15,553 (6.0)	1,621 (2.5)	0.171
Any difficult insertion, n (%)	24,666 (9.5)	4,648 (7.3)	0.080
Number of IUD insertions performed by provider, mean (SD)	44.7 (36.1)	43.5 (31.8)	0.035
Concomitant gynecologic procedure, n (%)	23,104 (8.9)	2,662 (4.2)	0.192
Calendar year of IUD insertion, n (%)			
2001 - 2009	12,233 (4.7)	3,516 (5.5)	0.036
2010	24,346 (9.4)	6,891 (10.8)	0.048

Characteristics	IUD Type		Unweighted Absolute Standardized Differences[a]
	LNG-IUD (N = 259,234)	Copper IUD (N = 63,664)	
2011	25,918 (10.0)	6,450 (10.1)	0.004
2012	28,878 (11.1)	7,378 (11.6)	0.014
2013	27,243 (10.5)	6,855 (10.8)	0.008
2014	27,342 (10.5)	6,404 (10.1)	0.016
2015	29,966 (11.6)	7,256 (11.4)	0.005
2016	33,202 (12.8)	7,678 (12.1)	0.023
2017	37,593 (14.5)	8,406 (13.2)	0.038
2018	12,513 (4.8)	2 830 (4.4)	0.018

485 IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine system; SD = standard
486 deviation.

487 [a] Standardized differences assess the difference between groups.[15] An absolute value of < 0.2 is
488 generally considered as small.[16]

489 **Table 2. Crude Incidence Rates per 1,000 Person-Years and 1-Year and 5-Year**

490 **Crude Cumulative Incidence Rates for IUD-Related Uterine Perforation and**

491 **Expulsion, by IUD Type**

IUD Type	No. of Insertions	Person-Years	No. of Events	Crude Incidence Rate per 1,000 Person-Years (95% CI)	Crude Cumulative Incidence,% (95% CI) 1 Year	5 Years
Uterine perforation						
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)
IUD expulsion						
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 IUD	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)

492 CI = confidence interval; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine

493 system; Cu-IUD = Copper intrauterine system.

494

495

496 # FIGURE CAPTIONS

497 **Figure 1. Study Cohort**

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

501 **Figure 2. Crude Cumulative Incidence of (A) Uterine Perforation and (B) IUD**
502 **Expulsion, by IUD Type**

503 **A. Uterine Perforation**

504 IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing int auterine system.

505 **B. IUD Expulsion**

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

507 **Figure 3. Crude and Propensity Score–Adjusted Hazard Ratios (Log Scale) for**
508 **LNG-IUDs Compared With Copper IUDs: (A) Uterine Perforation and (B) IUD**
509 **Expulsion**

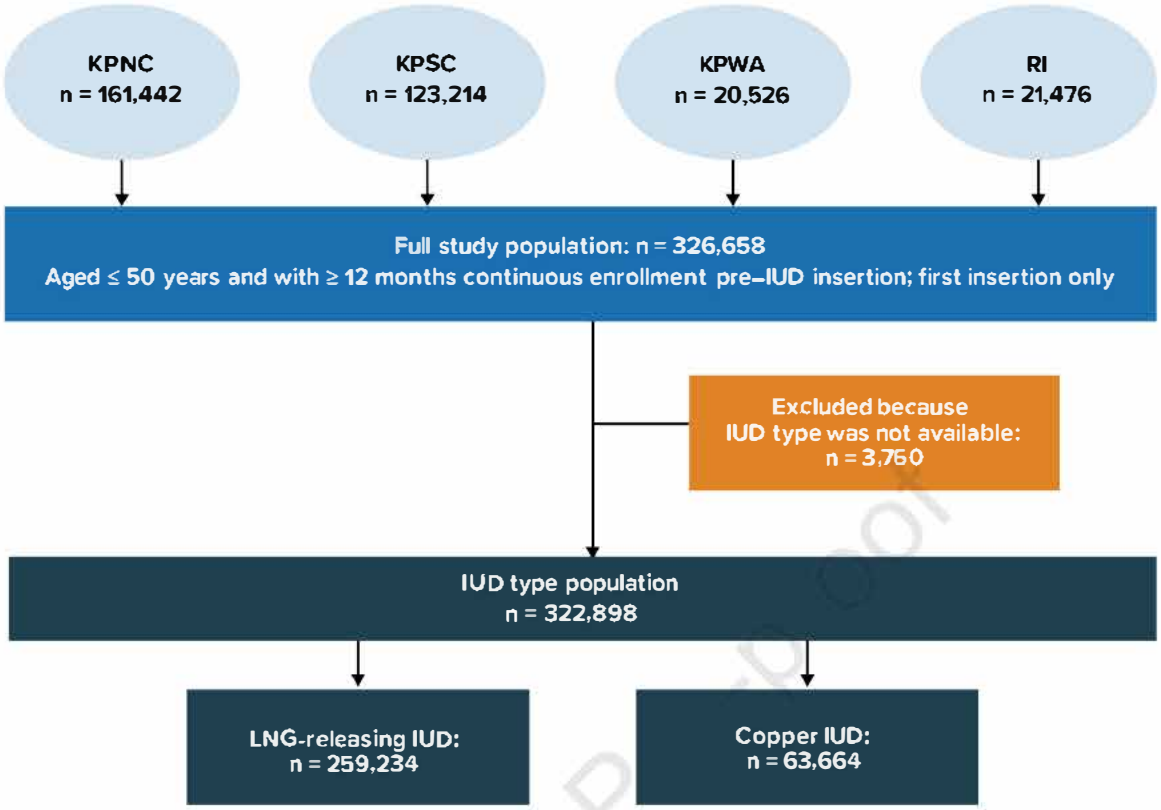
510 **A. Uterine Perforation**

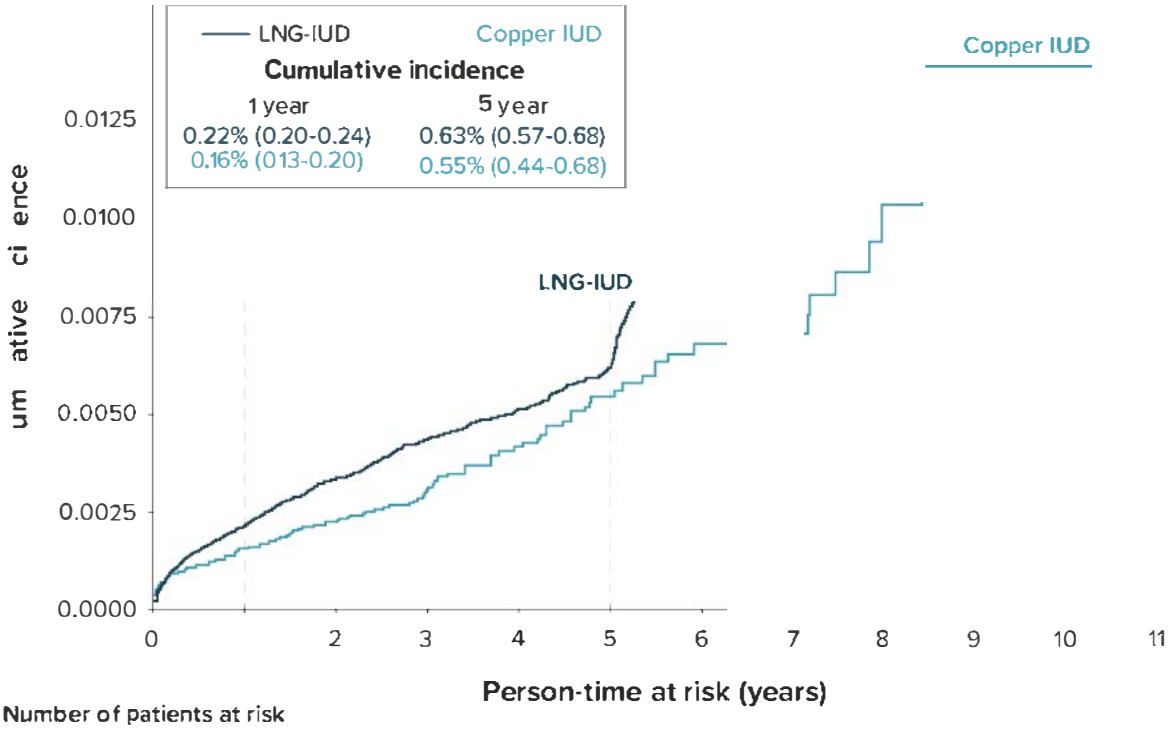
511 **B. IUD Expulsion**

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

513 Adjusted HRs were calculated using the Cox model weighted with propensity score overlap weights. The
514 following variables were included in the propensity score models for adjustment for both perforation and
515 expulsion outcomes: postpartum status (4 categories), breastfeeding status, menorrhagia diagnosis in the
516 last 12 months, age (tertiles), race/ethnicity, calendar year of index date (categorical), BMI (categorical),
517 dysmenorrhea, uterine fibroids, parity (0, > 0, or missing), cesarean delivery at any time before index
518 date, live birth for the most recent delivery, concomitant gynecologic procedure, indicator of difficult IUD

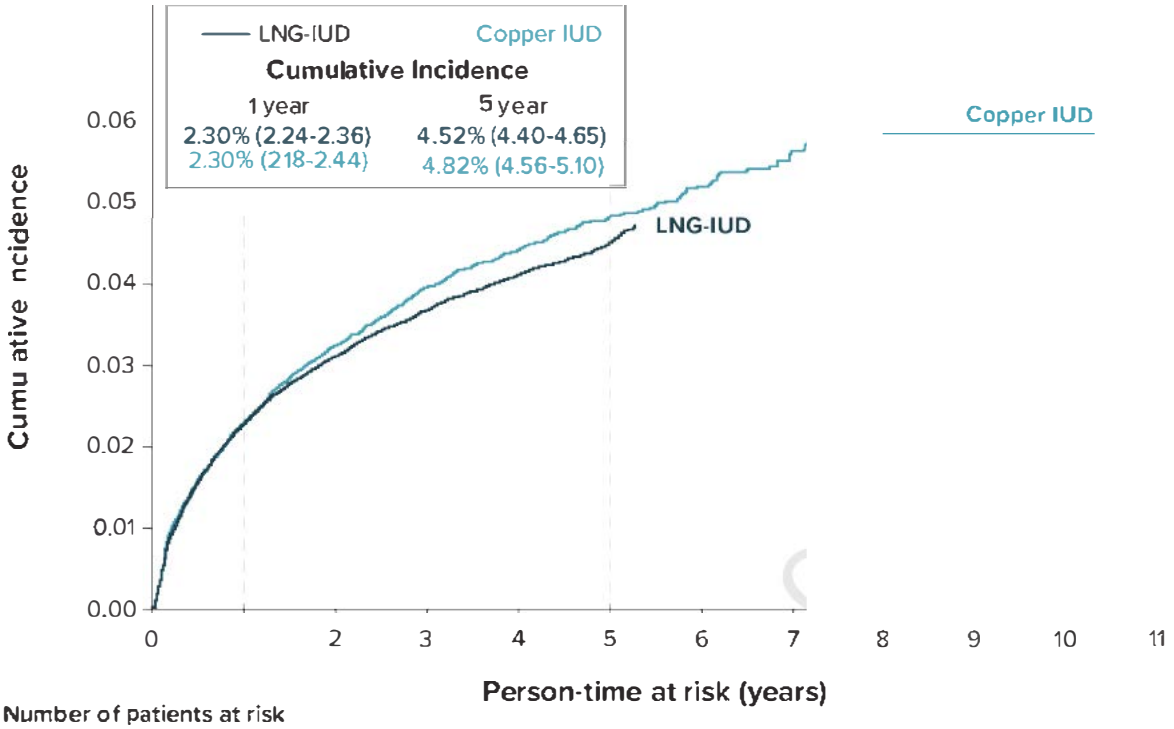
insertion, provider experience (quartiles), and research site. For the propensity score model for perforation, additional variables included recent smoking, duration of look-back period (quartiles), and cesarean delivery for most recent delivery. To further adjust for postpartum categories after a lack of balance in initial propensity score models, an interaction of postpartum timing (4 categories) by site was added for the expulsion outcome.





Number of patients at risk

LNG-IUD	259,234	157,327	100,947	67390	44,901	22,708	0					
Copper IUD	63,664	37,241	22,888	14,862	9,968	6,547	4,052	2,272	1,012	240	40	0



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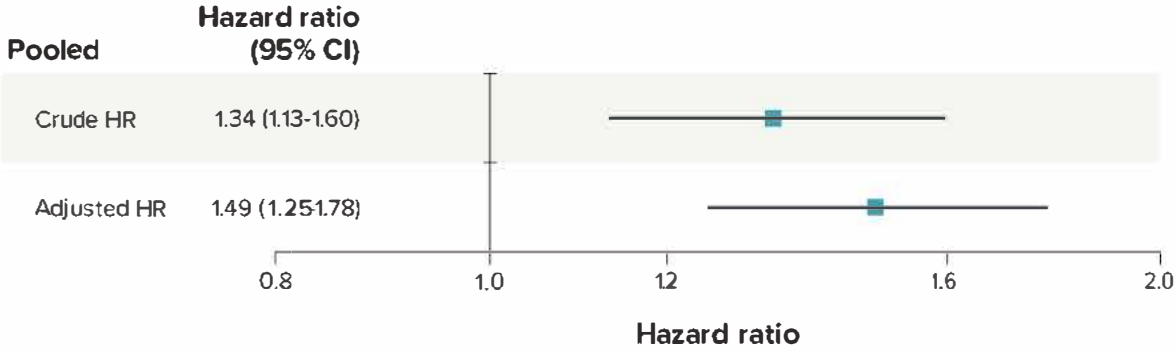
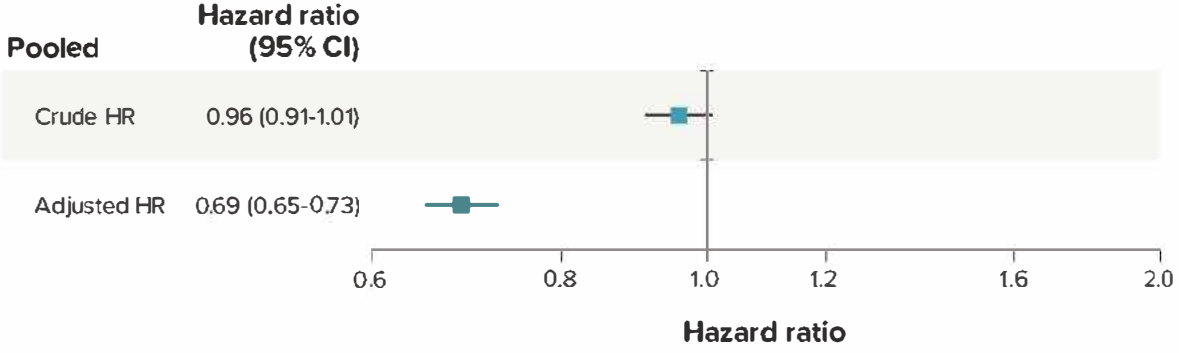

Pooled
Hazard ratio (95% CI)
Crude HR
1.34 (1.13-1.60)
Adjusted HR
1.49 (1.25-1.78)
0.8
1.0
1.2
1.6
2.0
Hazard ratio


Pooled
Hazard ratio (95% CI)
Crude HR
0.96 (0.91-1.01)
Adjusted HR
0.69 (0.65-0.73)
0.6
0.8
1.0
1.2
1.6
2.0
Hazard ratio