Contraception 105 (2022) 19–25

Contents lists available at ScienceDirect

Contraception

journal homepage: www.elsevier.com/locate/contraception

Original research article

Ectopic pregnancy prevention: Further evidence of benefits of prescription contraceptives☆,☆☆

Tina Raine-Bennett[a,b,1,*], Michael J. Fassett[c,d], Malini Chandra[a], Mary Anne Armstrong[a], Jiaxiao M. Shi[e], Vicki Y. Chiu[e], Amy Alabaster[a], Stacey Alexeeff[a], Fagen Xie[e], Theresa M. Im[e], Alex Asiimwe[f], Federica Pisa[f], Darios Getahun[b,e]

[a] The Division of Research, Kaiser Permanente Northern California, Oakland, CA, Unites States
[b] Department of Health Systems Science, The Bernard J. Tyson Kaiser, Permanente School of Medicine, Pasadena, CA, Unites States
[c] Department of Obstetrics and Gynecology, Kaiser Permanente West Los Angeles Medical Center, Los Angeles, CA, Unites States
[d] Department of Clinical Science, The Bernard J. Tyson Kaiser, Permanente School of Medicine, Pasadena, CA, Unites States
[e] Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, CA, Unites States
[f] Bayer A.G., Berlin, Germany

A R T I C L E I N F O

Article history:
Received 12 June 2021
Received in revised form 5 September 2021
Accepted 13 September 2021

Keywords:
Contraception
Ectopic pregnancy
Pregnancy prevention
Electronic health records

A B S T R A C T

Objective: To estimate the incidence of ectopic pregnancy (EP) associated with prescription contraceptive use.
Study Design: We performed a retrospective cohort study of women aged 15 to 44 years at Kaiser Permanente Northern and Southern California during 2010 to 2019. We identified EPs and prescription contraceptive use from diagnosis, procedural, and medication codes, and natural language processing of clinical notes from electronic health records. Contraceptive use categories included combined hormonal contraceptives, intrauterine devices, depot-medroxyprogesterone acetate (DMPA), progestin-only pills (POPs), implants, no method after recent discontinuation of a prescription contraceptive in the last 12 months, and no method after discontinuation of a prescription contraceptive more than 12 months ago or no use of prescription contraceptives during the study period. Contraceptive use was updated as women started, stopped, or changed methods. An EP was attributed to a contraceptive method if it occurred 14 days after starting and up to 42 days after stopping a method. Age-adjusted EP incidence and 95% confidence intervals (CI) were estimated per 10,000 woman-years overall and by contraceptive category.
Results: There were 11,436 EPs among 3,204,118 women with 11,909,842 woman-years of follow-up for an overall EP incidence of 9.5 per 10,000 woman-years (95%CI 9.3–9.6). The majority of EPs (9662; 84.5%) occurred during no prescription contraceptive use. EP incidence was lowest during DMPA (1.8 per 10,000 woman-years [95%CI 1.2–2.5]) or implant (2.0 per 10,000 woman-years [95%CI 1.2–3.3]) use, and higher during POP use at 15.2 (95%CI 12.2–19.6); however, incidence was highest after recent discontinuation of a prescription contraceptive (20.6 per 10,000 woman-years [95%CI 19.7-21.4]).
Conclusions: EP incidence is lower with prescription contraceptive use than with nonuse.
Implications: All prescription contraceptives, including POPs are protective of EP.

1. Introduction

Ectopic pregnancy (EP), defined as a pregnancy that implants outside of the uterus, accounts for 1% to 2% of recognized pregnancies and is associated with short- and long-term sequelae including subsequent EPs and infertility, and in rare cases maternal mortality [1–3]. Available contraceptive methods reduce the absolute risk of EP by lowering the risk of pregnancy overall; however, when there is method failure, pregnancies in women using contraceptives are more likely to be ectopic than pregnancies in women who were not using contraceptives [4]. The risk of EP may vary depending on

☆ *Declaration of Competing Interest*: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
☆☆ *Funding*: This work was supported by grants to Kaiser Permanente Northern and Southern California from Bayer AG. Co-authors from Bayer AG contributed to study design, interpretation of data, and preparation of the manuscript
* Corresponding author.
E-mail address: traine-bennett@medicines360.org (T. Raine-Bennett).
[1] Dr. Raine-Bennett was employed at the listed affiliation (KPNC) until June 30th, 2021 and the manuscript was submitted June 14th, 2021.

https://doi.org/10.1016/j.contraception.2021.09.007
0010-7824/

the mechanism of action of the method. Failure of methods such as combined hormonal contraceptives, which act primarily by inhibiting ovulation, may be less likely to lead to an EP than failure of methods such as intrauterine devices or progestin-only methods, which act locally in the cervix, uterus, or fallopian tube, and thus when conception occurs on the method the local contraceptive effect may lead to implantation outside the uterus [5]. Information on the absolute risk of EP while using different contraceptive methods relative to when contraceptives are not used is beneficial for expressing benefits and risks of undesired outcomes and can guide clinical decision-making.

Comparative data on the risk of EP with the use of various methods is limited. Many of the studies are dated, based on international populations or selected methods, or have flawed study designs [6–9]. Case-control studies can lead to bias and overestimation of EP risk associated with contraceptives, if limited to contraceptive method users only, or if inappropriate controls such as women with live births are selected [10]. In an epidemiological surveillance study from 1990, Zhang et al. demonstrated that the incidence of EP varied by contraceptive methods used by women, with the lowest incidence in women with female sterilization at 0.18 per 1000 women, and the highest incidence in women using natural family planning at 2.43 per 1000 women [7].

In the last decade there has been a change in the mix of contraceptive methods used, with greater use of implants and IUDs, particularly hormonal IUDs, making it important to understand the relative risks and benefits of different methods [11]. The goal of this study was to assess the incidence of EP associated with use or nonuse of prescription contraceptives in a community-based population of US women in the last decade. We hypothesized that the lowest EP incidence would be seen with the most effective contraceptives, particularly, long-acting reversible contraceptives - intrauterine devices and implants.

2. Materials and methods

2.1. Study population

We conducted a retrospective cohort study to examine EP incidence associated with prescription contraceptive use among women aged 15 to 44 enrolled in Kaiser Permanente Northern (KPNC) and Southern (KPSC) California health plans during 2010 to 2019. KPNC and KPSC currently provide care to over 9 million health plan members across the state representing approximately 47% of the commercially insured and 29% of the publicly insured population [12]. Members receive their care almost exclusively from Kaiser Permanente physicians and allied staff in the medical centers and medical office buildings owned or operated by the health plan, of which all utilize the EPIC electronic health record (EHR). To be included in the study women had to be enrolled in a health plan for at least 1 month and have at least 12 months of continuous membership (with less than a 93-day gap) as a look-back window to capture information on contraceptive use and past history. Women were excluded if they had a history of hysterectomy or bilateral salpingo-oophorectomy or oophorectomy. This study was approved by the Institutional Review Board of the Kaiser Foundation Research Institute with waiver of consent. KPSC also received approval from the California Health and Human Services Agency and California Department of Public Health Center for Health Statistics and Informatics.

2.2. Study outcomes and variables

The index date, the first date for study observation, was defined as the first day from January 1, 2010, through December 31, 2019, on which a woman had been enrolled in the health plan continuously for 12 months. A woman had to be enrolled from January 1, 2009, or earlier to have an index date of January 1, 2010. We identified EPs and time periods of prescription contraceptive use from the EHR based on previously validated algorithms. The identification of EP cases was based on a classification algorithm, that incorporated International Classification of Diseases Diagnosis and Procedure codes (ICD-9 and ICD-10), and Current Procedural Technology (CPT-4) codes for EP, and medication codes for methotrexate injections [13]. The EP diagnosis date was defined as the date of the first encounter with an EP code. Multiple encounters with EP codes occurring within a 180-day period from the first encounter with an EP code were considered part of the same pregnancy episode. For women who had more than 1 EP during the study period, each EP was included. The accuracy of EP case ascertainment using the algorithm was previously validated and found to have a sensitivity of 97.6%, specificity of 84.9%, positive predictive value of 92.9%, and negative predictive value of 94.6% [13].

Prescriptive contraceptive exposure time was determined using another algorithm that identified time from start to discontinuation of methods in the EHR. Contraceptives of interest for the study included levonorgestrel- (LNG), copper- (CU), and intrauterine devices (IUDs) of unknown type, combined oral contraceptive pills (COC), progestin-only oral contraceptive pills (POP), the depot-medroxyprogesterone acetate (DMPA) injection, the contraceptive implant, transdermal patch, and vaginal ring. COCs, the transdermal patch, and vaginal ring were combined into 1 category of combined hormonal contraceptives (CHCs) because they have the same mechanism of action and relatively smaller numbers of women in our cohort used patches and rings. The algorithm, which has been described previously, identified each woman's periods of contraceptive use from the index date through the end of enrollment or December 31, 2019, which ever occurred first [14]. For women who had health plan enrollment gaps of more than a 93-days, we allowed up to 3 enrollment periods. A 12-month look-back period was required for each enrollment. Chart review was performed on a stratified random sample of women in the population to validate the accuracy of the contraceptive use algorithm. We looked for evidence of use of dispensed methods in subsequent encounters or evidence of undocumented IUD expulsions or device removals. The overall positive predictive value (PPV) of the algorithm (compared to the gold standard of chart review) was 93% (95% CI 90.8−94.7). PPV by method was CU-IUD 100% (95% CI 93.5−100); LNG-IUD 96.6% (95% CI 91.4−99.1); unknown type IUD 88.5% (95% CI 69.9−97.6); COC 91.9% (95% CI 86.5−95.6); POP 87.3% (95% CI 77.3−94.0); patches or rings 91.2% (95% CI 80.7−97.1); implant 83.8% (95% CI 73.4−91.3); DMPA 97.8% (95% CI 88.5−99.9). PPV women with no prescription method use was 97.1% (95% CI 91.8−99.4) [14].

2.3. Analysis

Data on age, self-reported race/ethnicity, and health plan enrollment were obtained from administrative databases. Summary statistics were calculated for women in the study population including mean age and standard deviation (SD) and by age group (15−19, 20−29, 30−34, ≥35 years) at start of the first method, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian/Pacific Islander, Other/Unknown) and median family household income obtained from 2010 census block data (< $30,000, $30,000−$49,999, $50,000−$69,999, $70,000−$89,999, ≥ $90,000). *p* values are not reported for the summary statistics since we were not hypothesis testing and differences are typically statistically significant due to the large sample size. Demographic information of women who were excluded from the cohort was compared to the study population using Chi-square statistics. Two-sided p values < 0.05 were considered statistically significant.

Over time a woman may have used no method, or 1 or more methods with 1 or more periods of method use. Contraceptive use was updated as women started, stopped, or changed methods. During time periods when women used more than 1 method, observation time was assigned to only 1 method using a hierarchy which prioritized IUDs, implants, and DMPA injections as use of these methods was identified from procedural codes and were more likely to be the method used. During time periods when women did not use prescription contraceptive methods, they may have been sexually active and used nonprescription contraceptives, had periods of abstinence, or were never sexually active. Since information on sexual activity is not consistently documented in the EHRs, to identify time periods when women may have been more likely to be sexually active and thus at risk for EP, we separated time periods with no prescription contraceptive use into 2 categories: (1) recent discontinuation - no method after discontinuation of a prescription contraceptive in the last 12 months; and (2) remote or no use during the study period - no method after discontinuation of a prescription contraceptive more than 12 months ago or no use of a prescription contraceptive during the study period. We hypothesized that periods of time when women were not using a prescription contraceptive method but had discontinued a method in the last 12 months would be a proxy for probable sexual activity. Women were considered not at-risk for EP during pregnancies that ended in a live birth or induced abortion; they were temporarily censored for the gestational period which was calculated from the estimated gestational age and delivery date for live births or was assigned 42 days for induced abortions. Women were also censored for 30 days after a live birth, induced abortion, or EP.

The outcome of interest was the occurrence of EP, and the exposure of interest was method of contraception used or no method when the EP occurred. An EP is typically diagnosed at 6 to 7 weeks after conception. Therefore, to identify contraceptive methods a woman would have used at the time of conception, EPs that were identified during use or within 42 days of stopping a method were considered to have occurred during use of that method. An EP also had to be identified at least 14 days after starting a method to be attributed to the method since conception would have occurred earlier, and to minimize the chance of identifying methods that were started immediately after EP treatment. When 2 methods were identified within 42 days of the date of the EP, the EP was attributed to the first method. EP incidence per 10,000 woman-years and 95% confidence intervals (95% CI) were estimated for each contraceptive method category and for the nonuse categories. We used the percent distribution of women by age group in the middle of the study period in 2014 as a standard to obtain the age-adjusted incidence. Finally, we conducted a sensitivity analysis limited to women who enrolled in health plans with an index date from 2010 to 2015 to minimize bias due to increased potential for less observation time for women enrolled in later years. Data were analyzed using Statistical Analysis System (SAS v9.4; SAS Institute, Cary, NC).

3. Results

There were 4,011,435 women who were enrolled in a KPNC or KPSC health plan from 2010 to 2019; slightly over half were at KPSC ($n = 2{,}155{,}910$; 53.7%) (Fig. 1). After excluding women who lacked continuous health plan membership for 12 months before the index date and women who were known not to be at risk for pregnancy, there were 3,204,118 women with 11,909,842 woman-years of follow-up. Women who were excluded were more likely to be in the 20 to 29 age group at index (40.8% in the excluded group vs 33.1% in the study cohort, $p < 0.0001$) and more likely to have unknown/missing race-ethnicity (35.0% in the excluded group, 9.8% in the study cohort, $p < 0.0001$). They were also more likely to have median household income less than $50,000 (28.0% vs 26.1%, $p < 0.0001$).

The demographic characteristics of women in the study population by prescription contraceptive used are provided in Table 1. The mean time women were enrolled in the health plan was 3.7 ± 2.9 years. CHCs were the most popular methods with them being the only methods used by 22.4% of women during the study period. Women who used CHC only were most likely to have been 20-29 years old (43.7%) and non-Hispanic white (40.3%). Women who used IUDs only were least likely to be adolescents (5.2%) and most likely to be 35 years and older (35.5%). Women who used DMPA only were most likely to be Hispanic (45.0%). Half (53.7%) of women did not use a prescription contraceptive method during the study period; women who were 35 years or older (34.2%) at index were more likely to have not used a method during the study period.

There were 11,436 EPs during 11,909,842 woman-years of follow-up for an overall EP incidence of 9.5 per 10,000 woman-years (95% CI 9.3−9.6) (Fig. 1). The vast majority of EPs ($n = 9{,}662$; 84.5%) occurred during periods of no prescription contraceptive use. Prescription contraceptive method use periods were identified for a small fraction of the total study period. There were 3,375,425 woman-years of prescription contraceptive use observation time and 8,534,416 women-years of nonuse observation time. EP incidence during contraceptive use (4.7 per 10,000 woman-years [95% CI 4.5−4.9]) was approximately half the incidence during prescription contraceptive nonuse (11.8 per 10,000 woman-years [95% CI 11.5−12.0]). EP incidence was highest during nonuse following discontinuation of a prescription contraceptive in the last 12 months (20.6 per 10,000 woman-years [95%CI 19.7−21.4]), which was 2-times higher than the EP incidence with no use without use of a prescription contraceptive method in the last 12 months or at all during the study period (10.3 per 10,000 woman-years [95%CI 10.1−10.5]) (Fig. 1).

The incidence of EP by contraceptive method is provided in Table 2. Of the 1,774 EPs that were identified during prescription contraceptive use, the lowest number of EPs occurred during DMPA or implant use ($n = 33$ and 39 respectively), with an incidence per 10,000 woman-years of 1.8 (95% CI 1.2−2.5) and 2.0 (95% CI 1.2−3.3) respectively. EP incidence during prescription contraceptive use was highest for the POP at 15.2 (95% CI 12.2−19.6); however, this incidence was lower than the incidence after recent discontinuation of a prescription contraceptive in the last 12 months (20.6 [95% CI 19.7−21.4]). EP incidence for the LNG-IUD (3.7 [95% CI 3.2−4.4]) was lower than the incidence for the CU-IUD (7.8 [95% CI 6.4−9.9]); the confidence intervals did not overlap (Table 2).

There were 2,274,062 women with 10,442,118 woman-years of observation time who were enrolled in a health plan with an index date during 2010-2015 that were included in the sensitivity analysis (Table 3). The results of the sensitivity analysis were similar to the main analysis with an overall age-adjusted EP incidence of 9.4 [95% CI 9.2−9.6]; the highest EP incidence also occurred after recent discontinuation of a prescription contraceptive in the last 12 months (20.5 [95% CI 19.6−21.4]) and with POP use (14.5 [95% CI 11.5−19.3]).

4. Discussion

This retrospective study of women in a large integrated health care system during 2010 to 2019 revealed that EP incidence was lower during prescription contraceptive use than when there was no prescription contraceptive use, consistent with a protective effect for prescription contraceptives to prevent EP. Moreover, EP incidence varied by prescription contraceptive method, with the lowest incidence during DMPA or implant use, and higher incidence

Table 1
Demographics of the study population by prescription contraceptive use 2010 to 2019; Kaiser Permanente Northern and Southern California - N = 3,204,118.

	Total N = 3,204,118(%)	Only used combined hormonal contraceptives[a] n = 717,455(22.4)	Only usedIntrauterine devices n = 236,669 (7.4)	Only used DMPA n = 61,487(1.9)	Only usedProgestin-only pill n = 45,620 (1.4)	Only usedImplant n = 43,820 (1.4)	Used more than one method n = 379,494 (11.8)	No methods used n = 1,720,573 (53.7)
Woman-years Mean ± SD	3.7 ± 2.9	4.3 ± 2.9	4.4 ± 2.9	4.1 ± 2.8	3.7 ± 2.9	3.5 ± 2.6	5.9 ± 2.6	2.9 ± 2.6
Time on method (years) mean ± SD	2.6 ± 2.4	1.8 ± 2.0	2.9 ± 2.5	1.1 ± 1.5	0.6 ± 0.9	1.8 ± 1.6	3.3 ± 2.3	2.9 ± 2.6
Age at method start (years) mean± SD	28.3 ± 8.8	27.0 ± 7.8	31.4 ± 7.0	27.3 ± 8.3	31.8 ± 6.2	23.9 ± 6.5	26.0 ± 7.0	28.9 ± 9.6
15–19	22.4	21.6	5.2	24.1	2.8	31.5	22.7	25.2
20–29	33.1	43.7	35.1	37.0	33.3	49.3	45.4	25.2
30–34	16.6	15.1	24.3	15.6	30.2	11.4	18.8	15.5
≥35	28.0	19.6	35.5	23.4	33.7	7.8	13.1	34.2
Race/Ethnicity								
Non-Hispanic White	32.2	40.3	37.0	25.0	37.5	27.0	38.0	27.1
Non-Hispanic Black	7.4	6.5	7.5	15.9	7.4	8.9	9.2	7.1
Hispanic	34.4	30.9	36.4	45.0	33.3	47.5	37.2	34.4
Asian/Pacific Islander	16.1	15.1	14.2	9.2	18.1	10.5	11.8	18.1
Other/Unknown	9.8	7.2	5.1	4.9	3.8	6.2	3.8	13.3
Income[b]*, US Dollars*								
< $30,000	4.3	3.6	4.4	6.7	3.7	5.7	4.2	4.5
$30,000–$49,999	21.8	19.1	21.7	28.7	20.3	26.3	21.6	22.6
$50,000–$69,999	26.7	26.2	26.6	29.4	26.4	28.5	27.4	26.7
$70,000–$89,999	21.6	22.6	21.6	19.2	22.5	20.2	22.1	21.2
≥ $90,000	25.3	28.3	25.6	15.8	26.9	19.1	24.5	24.7
Missing	0.2	0.2	0.1	0.1	0.2	0.2	0.1	0.3

DMPA, depot medroxyprogesterone acetate; SD, standard deviation.
Data are column percents unless otherwise noted.
[a] Combined hormonal contraceptives includes combined oral contraceptives, the transdermal patch, and the vagina ring.
[b] Family household median income obtained from 2010 census block data.

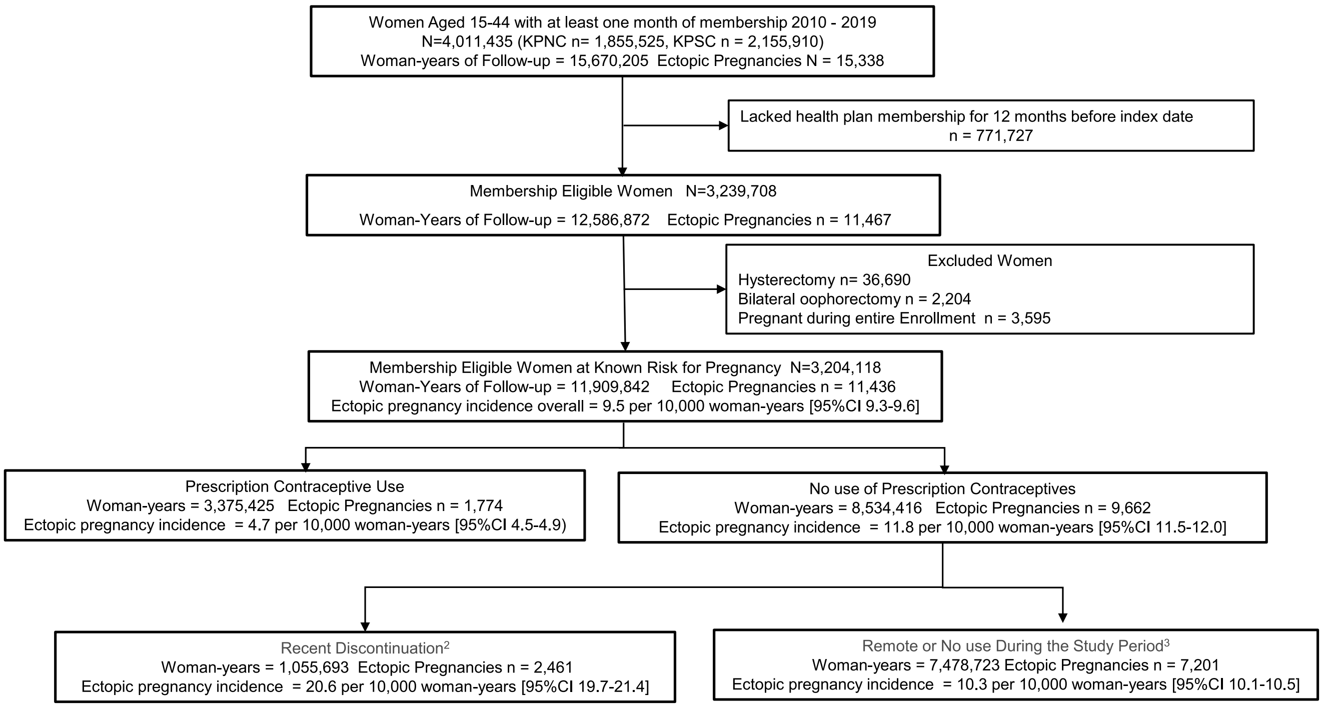

Fig. 1. Ectopic pregnancy incidence in women with prescription contraceptive use and nonuse 2010 to 2019; Kaiser Permanente Northern and Southern California.

Table 2
Ectopic pregnancies incidence by prescription contraceptive method 2010-2019; Kaiser Permanente Northern and Southern California – $N = 3{,}204{,}118$.

Method	Number of ectopic pregnancies	Woman-years	Incidence per 10,000 woman years[a]	95% confidence interval
Combined hormonal contraceptive[b]	935	1,811,306	4.8	4.5–5.2
Levonorgestrel IUD	306	779,965	3.7	3.2–4.4
Copper IUD	195	243,918	7.8	6.4–9.9
IUD Type unknown	62	73,584	8.0	6.0–10.9
Depomedroxyprogesterone acetate	33	160,488	1.8	1.2–2.5
Progestin-only oral contraceptive	204	118,318	15.2	12.2–19.6
Implant	39	187,844	2.0	1.2–3.3
No method:				
Recent discontinuation[c]	2461	1,055,693	20.6	19.7–21.4
Remote or no use during the study period[d]	7201	7,478,724	10.3	10.1–10.5
Overall	**11,436**	**11,909,842**	**9.5**	**9.3–9.6**

[a] Age-adjusted incidence based on the age distribution of women aged 15-44 years in 2014.
[b] Combined hormonal contraceptives includes combined oral contraceptives, the transdermal patch, and the vagina ring.
[c] No method after discontinuation of a prescription contraceptive in the last 12 months.
[d] No method after discontinuation of a prescription contraceptive more than 12 months ago or no use of prescription contraceptives during the study period.

Table 3
Ectopic pregnancy incidence by prescription contraceptive method 2010-2019; Kaiser Permanente Northern and Southern California – $N = 2{,}274{,}062$.

Method	Number of ectopic pregnancies	Woman-years	Incidence per 10,000 woman years[a]	95% confidence interval
Combined hormonal Contraceptive[b]	837	1,620,778	4.8	4.5–5.2
Levonorgestrel IUD	273	713,765	3.8	3.2–4.5
Copper IUD	182	223,621	7.9	6.5–10.0
IUD Type unknown	51	64,923	8.0	5.8–11.2
Depomedroxyprogesterone acetate	29	146,223	1.7	1.1–2.5
Progestin-only oral contraceptive	182	105,583	14.5	11.5–19.3
Implant	31	152,992	2.0	1.2–3.4
No method:				
Recent discontinuation[c]	2,189	945,278	20.5	19.6–21.4
Remote or no use during the study period[d]	6,259	6,468,957	10.3	10.0–10.5
Overall[a]	**10,033**	**10,442,118**	**9.4**	**9.2–9.6**

Sensitivity Analysis women with enrollment start 2010 to 2015.
[a] Age-adjusted incidence based on the age distribution of women aged 15 to 44 years in 2014.
[b] Combined hormonal contraceptives includes combined oral contraceptives, the transdermal patch, and the vagina ring.
[c] No method after discontinuation of a prescription contraceptive in the last 12 months.
[d] No method after discontinuation of a prescription contraceptive more than 12 months ago or no use of prescription contraceptives during the study period.

during POP use. The highest EP incidence, however, was observed after recent discontinuation of a prescription contraceptive in the last 12 months. During the study period, we did not have information about sexual activity or use of over-the-counter contraceptive methods. We suspect that periods of nonuse following recent discontinuation were periods when women were more likely to have been sexually active compared to periods after remote discontinuation, or no use of a prescription contraceptive during the study period. If women were largely trying to conceive after discontinuing contraceptives, then one would expect the EP incidence to be highest. If women were not sexually active, used condoms, were having unprotected sex, or a combination, after recent discontinuation of contraceptives, which is likely, then our estimate of EP incidence after recent discontinuation is probably conservative. This is one of the only and largest studies to document estimates of EP incidence during time periods of prescription contraceptive use and nonuse and the protective effect of contraceptive use on EP.

The only other population-based study that we are aware of that assessed EP incidence for contraceptive users and nonusers was the study by Zhang et al. which also demonstrated that current contraceptive users have a lower incidence of EP than noncontraceptive users [7]. In their population of approximately 2.7 million women of reproductive age living in Beijing, EP incidence for married women using no contraceptives was 1.80 per 1000 compared to 0.54 per 1000 married women using contraceptives [7]. A limitation of this study is that it was conducted in a racially homogeneous study population. Our contemporary EP incidence rates are similar to their rates; however, we provide more granularity by oral contraceptive pill and IUD type.

Other studies of specific methods from clinical trial data have found that the incidence of EP is higher for the POP, and have suggested that the incidence may be higher than that of women not using contraceptives [4]. While our data also demonstrates higher incidence of EP with POP use, the incidence of EP with POP use was lower than the incidence with recent discontinuation of prescription contraceptives in the last 12 months. POPs containing norethindrone do not consistently inhibit ovulation, and they are less effective than CHCs, the implant, and DMPA, which may explain the higher incidence rate of EP in comparison to CHCs and other progestin-only methods [15]. In addition, previous in vitro studies have shown that progesterone and levonorgestrel suppress tubal ciliary beat frequency and smooth muscle contractions in the fallopian tube, which may facilitate implantation of an embryo in the fallopian tube [16,17]. Schultheis et al. did a comparative analysis of EP incidence with use of contraceptive methods in the Contraceptive CHOICE study, a prospective cohort of women who were provided no-cost contraception and followed for 3 years [18]. They also concluded that women using all methods had lower risk of EP than women not using methods or barrier methods; however, the analysis did not include the POP and was limited by small number of EPs ($n = 13$) in the study. Our results corroborate findings of the prospective observational study by Heinemann et al. that suggest the incidence of EP is higher with the CU-IUD than the LNG-IUD [19].

Our study has several strengths in addition to a large number of EPs. We used validated algorithms which demonstrated good accuracy for detecting the exposures and outcome of interest [13,14]. The study was performed within a large, racially diverse integrated health care system with access to pharmacy databases and clinical information allowing us to capture contraceptive use and EP outcomes. The population is broadly representative of the overall population except for individuals at the lower and upper extremes of income [20].

Our study also has limitations. The study may not be generalizable to noninsured populations in other health care systems. We used pharmacy records, which provides information on methods dispensed not actual use, to determine the exposure to oral contraceptives, transdermal patches, and vaginal rings. In contrast to methods that are initiated by a provider with a procedure, we cannot know for certain if women actually used methods that were identified from pharmacy records. A validation study using chart review to confirm evidence of contraceptive method use demonstrated 84% to 100% accuracy of electronically abstracted methods. Accuracy for prescribed methods was lower than methods which required procedures for initiation and discontinuation [14]. Accuracy of electronic abstraction of POP and COC use was similar; however, shorter time of POP use may have led to decreased ability to document nonuse of dispensed POPs and overestimation of the accuracy of electronic abstraction for POPs. We did not estimate EP rate during use of more than 1 prescription method at a time because analysis with multiple combinations of methods would have been very difficult and the results would not have been meaningful given the small number of EPs that would have probably occurred while on more than 1 method. We were unable to identify IUD type when IUD insertions occurred before enrollment in the Kaiser Permanente health care system. This may have led to underestimation or overestimation of observation time for IUDs of unknown type as imputation of end dates for product expiration may have been less accurate. We assessed the incidence of EP among women using various prescription methods; however, we did not assess EP incidence among all women becoming pregnant on various methods. Estimating the number of pregnancies that occurred during contraceptive use, would require validation of all pregnancies including miscarriages, which is beyond the scope of this analysis. Information on sexual activity or use of nonprescription contraceptives is not consistently available as structured data in the EHR, which prevented us from being able to categorize periods when prescription contraceptives were not used. Furthermore, women may have used prescription contraceptives for noncontraceptive reasons and not have been sexually active, which would have led to underestimation of EP risk. We adjusted for age differences in the population; however, we did not conduct a multivariate analysis to assess whether contraceptive use is independently associated with EP risk after adjusting for potential confounders. Future studies are needed to assess risk associated with use of prescription contraceptive methods on EP risk after adjusting for potential confounders such as infertility treatments, history of tubal disease, and smoking.

In conclusion, utilizing population-based data we found that EP incidence was lower overall for women who used any prescription contraceptive method, and was lowest for women who used DMPA or implants. Even though EP incidence was higher during use of the POP, the incidence still appears to be lower after recent discontinuation of prescription contraceptives. These results support the overall benefits of prescription contraceptive use and provide comparative information that can be used to guide counseling for women at risk of EP considering contraceptive options. Future studies should investigate whether the protective effect remains for women with various risk factors.

.

References

[1] Committee on Practice B-GACOG practice bulletin no. 191: tubal ectopic pregnancy. Obstet Gynecol 2018;131(2):e65–77. doi:10.1097/AOG.0000000000002464.

[2] Creanga AA, Shapiro-Mendoza CK, Bish CL, Zane S, Berg CJ, Callaghan WM. Trends in ectopic pregnancy mortality in the United States: 1980-2007. Obstet Gynecol 2011;117(4):837–43. doi:10.1097/AOG.0b013e3182113c10.

[3] Lisonkova S, Tan J, Wen Q, Abdellatif L, Richter S, Alfaraj S, et al. Temporal trends in severe morbidity and mortality associated with ectopic pregnancy requiring hospitalisation in Washington State, USA: a population-based study. BMJ Open 2019;9(2):e024353. doi:10.1136/bmjopen-2018-024353.

[4] Furlong LA. Ectopic pregnancy risk when contraception fails. A review. J Reprod Med 2002;47(11):881–5 https://www.ncbi.nlm.nih.gov/pubmed/12497674, Accessed 13 June 2021.
[5] Li C, Zhang HY, Liang Y, Xia W, Zhu Q, Zhang D, et al. Effects of Levonorgestrel and progesterone on oviductal physiology in mammals. Reprod Biol Endocrinol 2018;16(1):59. doi:10.1186/s12958-018-0377-3.
[6] Franks AL, Beral V, Cates W Jr, Hogue CJ. Contraception and ectopic pregnancy risk. Am J Obstet Gynecol 1990;163(4 Pt 1):1120–3 http://www.ncbi.nlm.nih.gov/pubmed/2220914, Accessed 13 June 2021.
[7] Zhang Z, Weng L, Zhang Z, Jin X, Jing X, Zhang L, et al. An epidemiological study on the relationship of ectopic pregnancy and the use of contraceptives in Beijing–the incidence of ectopic pregnancy in the Beijing area. Beijing Collaborating Study Group for Ectopic Pregnancy. Contraception 1994;50(3):253–62 https://www.ncbi.nlm.nih.gov/pubmed/7805376, Accessed 13 June 2021.
[8] Nordstrom F, McTaggart J, Melander E, Altman D, Kopp Kallner H. Contraceptive use at the time of and after an ectopic pregnancy: a retrospective cohort study. Eur J Contracept Reprod Health Care 2020;25(2):147–50. doi:10.1080/13625187.2020.1726887.
[9] Li C, Zhao WH, Meng CX, Ping H, Qin GJ, Cao SJ, et al. Contraceptive use and the risk of ectopic pregnancy: a multi-center case-control study. PLoS One 2014;9(12):e115031. doi:10.1371/journal.pone.0115031.
[10] Weiss NS, Daling JR, Chow WH. Control ddefinition in case-control studies of ectopic pregnancy. Am J Public Health 1985;75(1):67–8 http://www.ncbi.nlm.nih.gov/pubmed/3966602, Accessed 13 June 2021.
[11] Daniels K, Abma JC. Current contraceptive status among women aged 15-49: United States, 2017-2019. NCHS Data Brief 2020(388):1–8 https://www.ncbi.nlm.nih.gov/pubmed/33151146, Accessed 13 June 2021.
[12] California Health Care Foundation. California Health Care Insurers: Large Insurers Remain on Top. https://www.chcf.org/publication/2019-edition-california-health-insurers-large-insurers/#related-links-and-downloads, Accessed 13 June 2021.
[13] Getahun D, Shi JM, Chandra M, Fassett MJ, Alexeeff S, IM TM, et al. Identifying ectopic pregnancy in a large integrated health care delivery system: algorithm validation. JMIR Med Inform 2020;8(11):e18559. doi:10.2196/18559.
[14] Armstrong MA, Chandra M, Getahun D, Fassett MJ, Shi JM, Alabaster AA, et al. Validation of an algorithm to identify hormonal contraceptive exposure in a large integrated health care delivery system database. ISPE Annual Meeting Abstracts. Pharmacoepidemiol Drug Saf 2021;30(Suppl 1):3–400 Accessed 13 June 2021. doi:10.1002/pds.5305.
[15] Curtis KM, Tepper NK, Jatlaoui TC, Berry-Bibee E, Horton LG, Zapata LB, et al. U.S. medical eligibility criteria for contraceptive use, 2016. MMWR Recomm Rep 2016;65(3):1–103. doi:10.15585/mmwr.rr6503a1.
[16] Mahmood T, Saridogan E, Smutna S, Habib AM, Djahanbakhch O. The effect of ovarian steroids on epithelial ciliary beat frequency in the human Fallopian tube. Hum Reprod 1998;13(11):2991–4. doi:10.1093/humrep/13.11.2991.
[17] Wanggren K, Stavreus-Evers A, Olsson C, Andersson E, Gemzell-Danielsson K. Regulation of muscular contractions in the human Fallopian tube through prostaglandins and progestagens. Hum Reprod 2008;23(10):2359–68. doi:10.1093/humrep/den260.
[18] Schultheis P, Montoya MN, Zhao Q, Archer J, Madden T, Peipert JF. Contraception and ectopic pregnancy risk: a prospective observational analysis. Am J Obstet Gynecol 2021;224(2):228–9. doi:10.1016/j.ajog.2020.10.013.
[19] Heinemann K, Reed S, Moehner S, Minh TD. Comparative contraceptive effectiveness of levonorgestrel-releasing and copper intrauterine devices: the European Active Surveillance Study for Intrauterine Devices. Contraception 2015;91(4):280–3. doi:10.1016/j.contraception.2015.01.011.
[20] Gordon N, Lin T. The Kaiser Permanente Northern California Adult Member Health Survey. Perm J 2016;20(4):34–42. doi:10.7812/TPP/15-225.