Observational Study Information

Acronym/Title	**Incidence and Trend of Ectopic Pregnancy 2009-2018 - A population-based Study (EPR Study)**
Report version and date	V1.0 15 November 2021
IMPACT study number	20257
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Study type / Study phase	Observational
Medicinal product	Hormonal (Levonorgestrel-releasing intrauterine systems) and non-hormonal intrauterine devices
Comparator / Reference therapy	Oral contraception, Depot medroxyprogesterone Acetate, Transdermal Patch, Vaginal Ring, Subdermal Implant
Study Initiator and Funder	Bayer AG, 13342 Berlin
Research question and objectives	
Country(-ies) of study	United States
Author	PPD PPD Kaiser Permanente Northern California 2000 Broadway Oakland, CA , USA

Confidentiality statement:

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1. Abstract

Acronym/Title	**Incidence and Trend of Ectopic Pregnancy 2009-2018 - A population-based Study (EPR Study)**
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Study Initiator and Funder	Bayer AG, 13342 Berlin
Report version and date **Author**	V 1.0 15 November 2021 PPD Kaiser Permanente Northern California
Keywords	Ectopic pregnancy, Intrauterine Device, hormonal Contraception, risk factors
Rationale and background	Incidence, diagnosis, and management of ectopic pregnancy underwent significant increases during the 1980's and '90s, and rates appeared to stabilize from 2000 to 2007. There is a consensus that available effective contraceptive methods reduce the absolute risk of ectopic pregnancy by lowering the risk of pregnancy overall. However, in the case of method failure, the risk of ectopic pregnancy varies by method. The goal of this project was to assess the feasibility of and generate data using electronic health records on ectopic pregnancy incidence trends and risk factors in women from Kaiser Permanente Northern California (KPNC) and Kaiser Permanente Southern California (KPSC) over the 10-year period from 2009-2018.
Research question and objectives	The study was designed to address the following research questions:

	• What is the incidence rate of ectopic pregnancy among women of reproductive age and among the subset of women with current hormonal and non-hormonal IUDs, combined (COC) and progestin-only (POP) oral contraceptive pills (OCP), and depot medroxyprogesterone (DMPA) method use? • What are the temporal trends in ectopic pregnancy incidence rates over the last decade overall and in women with current contraceptive use? • What are the potential risk factors associated with ectopic pregnancy in women with current IUD, OCP, and DMPA use? • What are the trends in management of ectopic pregnancy over the last decade? We also conducted a study to validate ectopic pregnancy case ascertainment for the current study using administrative, claims, and electronic health records.
Study design	To achieve the aims of this project, we conducted a population-based cross-sectional and retrospective cohort study of women of reproductive age at KPNC and KPSC using data abstracted from Kaiser Permanente's electronic health record (EHR), regional claims systems, and administrative databases.
Setting	The study was conducted at KPNC and KPSC, which represent the two largest of KP's nine regional integrated health care systems nationwide.
Subjects and study size, including dropouts	The source population included 3,922,877 women who were age 15 to 44 years from January 1, 2009 to December 31, 2018 who were enrolled in the KPNC and KPSC health plans for at least one month over the study period. The validation study included 500 randomly sampled women from the source population with at least one encounter with a diagnostic or procedure code for ectopic pregnancy.
Variables and data sources	Woman-time at risk was based on membership enrollment months during the study period using the membership databases. Pregnancies resulting in live birth were identified using perinatal databases and induced abortions using administrative and claims databases. Contraceptive use was ascertained based on evidence of exposure time in the EHR

	databases. Demographic and clinical risk factors were obtained from EHR records.
Results	From 2009 to 2018, 14,662 ectopic pregnancies (7,312 KPNC; 7,350 KPSC) were identified among 15,130,822 woman-years and 945,177 pregnancies, live births and induced abortions for an overall age-adjusted rate of 9.5 per 10,000 woman-years and 15.7 per 1,000 pregnancies. The ectopic pregnancy incidence rate per 1,000 pregnancies increased over the study period from 14.5 to 17.1 per 1,000 pregnancies; the rate was highest among women aged 40-44 years (23.6 per 1,000 pregnancies). Half of ectopic pregnancies were managed surgically (47.7% KPNC; 55.6% KPSC) and proportion managed surgically slightly increased over time. The vast majority (90%) of ectopic pregnancy occurred in women who did not use contraceptives at the time of conception. Among women with current contraceptive use, the incidence of ectopic pregnancy appeared highest for women with POP use with an overall age-adjusted rate of 14.8 per 10,000 woman-years. Medical factors that conferred the highest magnitude of risk were history of prior ectopic pregnancy (adjusted HR 4.23, 95% CI 2.82, 6.36; p <0.0001) and infertility (adjusted HR 4.79, 95% CI 3.98, 5.77; p<0.001).
Conclusion	Our findings from two large U.S. health care systems demonstrate that the incidence of ectopic pregnancy increased over the last decade and remains a significant source of reproductive health morbidity. Surgical management was utilized equally as frequent as medical treatment. Women with current contraceptive use appeared to have a lower incidence of ectopic pregnancy than the overall population of women, providing reassurance of the protective effect of contraceptives. Factors associated with tubal factor infertility remain the most significant predictors of ectopic pregnancy.

2. List of abbreviations

AE	Adverse Event
BMI	Body Mass Index
CI	Confidence Interval
COC	Combined OCP (estrogen and progestin)
DOR	Division of Research (KPNC)
CPT	Current Procedural Terminology
DMPA	Depot medroxyprogesterone acetate
EDC	Estimated Date of Confinement
EGA	Estimated Gestational Age
EHR	Electronic Health Record
EMA	European Medicine Agency
EP	Ectopic Pregnancy
EURAS	European Active Surveillance Study for Intrauterine Devices
FDA	Food and Drug Administration
ICD	International Classification of Diseases
HIPPA	Health Insurance Portability and Accountability Act
HMO	Health Maintenance Organization
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
IT	Information Technology
IUD	Intrauterine Device
KP	Kaiser Permanente
KPHC	Kaiser Permanente HealthConnect
KPNC	Kaiser Permanente Northern California
KPSC	Kaiser Permanente Southern California
N/A	Not Applicable
NDC	National Drug Code
NLP	Natural Language Processing
NPV	Negative Predictive Value
OCP	Oral Contraceptive Pill (all types)
OS	Observational Study
PID	Pelvic Inflammatory Disease
PMR	Post Market Research
POP	Progestin-only OCP
PPV	Positive Predictive Value
RDW	Research Data Warehouse
R&E	Department of Research and Evaluation (KPSC)
SAP	Statistical Analysis Plan
STI	Sexually Transmitted Infection
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

VDW	Virtual Data Warehouse

3. Investigators

Name	Role	Contact Information
Bayer – Project Sponsor		
PPD		E-mail: PPD Telephone: PPD Location: Berlin, Germany
		E-mail: PPD Telephone: PPD Location: Berlin, Germany
		PPD Telephone: PPD Location: Espoo, Finland
		PPD Telephone: PPD Location: Basel, Switzerland
		E-mail: PPD Telephone: PPD Location: Berlin, Germany
		E-mail: PPD Telephone: PPD Location: Wuppertal, Germany
Kaiser Permanente Northern California (KPNC)– Principal data source		
PPD		E-mail: PPD Telephone: PPD Location: Oakland, CA, USA
		E-mail: PPD Telephone: PPD Location: Oakland, CA, USA
		E-mail: PPD Telephone: PPD Location: Oakland, CA, USA

Kaiser Permanente Southern California (KPSC)– Research Partner, additional data source	
PPD	E-mail: PPD Telephone: PPD Location: Pasadena, CA, USA
	E-mail: PPD Telephone: PPD Location: Los Angeles, CA, USA

4. Other responsible parties

N/A

5. Milestones

Milestones for this study are summarized in Table 1

5.1 Table 1. Milestones

Milestone	Planned Date	Actual Date	Comments
Contract executed	June 2018	July 2018	
IRB approvals	August 2018	October 2018	KPSC ceded to KPNC
Delivery of Statistical Analysis Plan	February 2019	February 2019	
Start of data collection	March 2019	March 2019	
Protocol Amended to add Validation study		June 2019	Separate study protocol developed – led to delay in overall project as primary aims related to main outcome validation
End of data collection	September 2019	December 2019	Contraceptive algorithms were more time intensive than expected – additional validation will be done
Preliminary report of study results	December 2019	March 2020	The study end was extended to March 2020 with the addition of the Validation Study.
Delivery of final study report	July 2021	July 2021	Final report including post-hoc analysis module
Delivery of final study report – v1	November 2021	November 2021	Final report v1 including post-hoc analysis module

6. Study background and research question

Ectopic pregnancy, the implantation of a fertilized egg outside the uterus, can be an acute, life-threatening condition leading to future reproductive morbidity, including subsequent ectopic

pregnancy and infertility.[1] Trends in ectopic pregnancy are difficult to examine as women with ectopic pregnancies are increasingly managed in the outpatient setting either medically with injection methotrexate or surgically with laparoscopy.[2,3] As a result, surveillance is difficult. The latest year for which nationwide data from the U.S. Centers for Disease Control and Prevention (CDC) are available is 1992 when the estimated total number of ectopic pregnancies was 108,800 for a rate of 19.7 per 1,000 reported pregnancies.[4]

Using computerized data from KPNC, Van Den Eeden et al. found that the rate of ectopic pregnancy in 1997-2000 was similar to the national rate at 20.7 per 1,000 reported pregnancies and 1.03 per 1,000 women 15–44 years old.[5] Trabert et al. reported ectopic pregnancy rates using computerized data from Group Health Cooperative in Washington State from 1993-2007.[6,7] The age-adjusted ectopic pregnancy rate appeared to slightly decrease from 18.2 per 1,000 pregnancies in 1993-1995 to 15.3 per 1,000 pregnancies in 2005-2007 (p-value for trend was not significant).[7]

Risk for ectopic pregnancy is associated with two main factors: the probability of conception and, after conception, the probability of implantation of the fertilized ovum outside of the uterus.[8] The vast majority of published studies assessing risk factors for ectopic pregnancies are case-control studies because ectopic pregnancies are relatively uncommon.[9] Studies of risk factors have compared risk factors in women with an ectopic pregnancy with both pregnant and non-pregnant controls.[10] As a result studies have yielding conflicting results depending on use of pregnant or non-pregnant controls.[10] The selection of women with live births as controls is appropriate if the hypothesis does not relate to exposures that prevent pregnancy (e.g., current contraceptive use). For a number of other possible risk factors for ectopic pregnancy, whether pregnant or nonpregnant controls are selected, it is difficult to minimize bias introduced by factors related to contraceptive practice.

Identified risk factors include tubal damage caused by infection, surgery, or disease (e.g. endometriosis), smoking, infertility, older age, and previous ectopic pregnancy.[1] There is a consensus that available effective contraceptive methods reduce the absolute risk of ectopic pregnancy by lowering the risk of pregnancy overall. However, when there is method failure, pregnancies in women using intrauterine devices (IUDs), some progestin-only contraceptives and tubal ligation are more likely to be ectopic than pregnancies in women in the general population and women using combined oral contraceptives or barrier methods.[11-13] The results of one of the largest prospective cohort studies suggest that current contraceptive users have a lower rate of ectopic pregnancy than non-contraceptive users. In an epidemiological surveillance in a population of approximately 2.7 million women of reproductive age living in Beijing, the incidence was 1.80 per 1,000 married women using no contraceptives compared to 0.54 per 1,000 married women using contraceptives. The rates were lowest for women with female sterilization at 0.18 per 1,000 married women. The rates were 2.43 per 1,000 married women using natural family planning, 0.65 for IUD users, 0.21 for OCP users, and 0.57 condoms/spermicides.[14]

In the last decade, there has been a change in the mix of contraceptive methods used, with greater emphasis on long acting reversible contraceptives, particularly hormonal IUDs. Comparative data on various methods is lacking; generation of evidence on ectopic pregnancy incidence and trends, and risk factors, including current use of various prescription contraceptives in the last decade, is of interest. Electronic health records provide a unique opportunity to conduct pharmacoepidemiologic studies as well as to investigate the natural history of selected disorders such as ectopic pregnancy while accounting for several potential confounding variables.

The overall goal of this study is to assess the incidence rate of ectopic pregnancy over the last decade in a representative population of US women and assess potential risk factors associated with ectopic pregnancy.

7. Research questions and objectives

The study is designed to address the following research questions:

- What is the incidence rate of ectopic pregnancy among women of reproductive age at KPNC and KPSC?
- What is the incidence rate of ectopic pregnancy among women with current IUD, OCP, and DMPA use?
- What are the temporal trends in ectopic pregnancy incidence rates over the last decade overall and in women with current prescription contraceptive use (hormonal and non-hormonal IUDs, combined OCPs [COC] and progestin-only OCPs [POP], and DMPA)?
- What are the potential risk factors associated with ectopic pregnancy in women of reproductive age at KPNC and KPSC?
- What are the trends in management of ectopic pregnancy over the last decade?

7.1.1 Primary Objectives

The primary aims of the study are:

1a. To describe the incidence and temporal trends of ectopic pregnancy during the past decade in women of reproductive age at KPNC and KPSC.

1b. To describe the incidence and temporal trends of ectopic pregnancy in women with current hormonal and non-hormonal IUDs, COCs and POPs, and DMPA use.

1c. To describe the incidence of ectopic pregnancy during current contraceptive use and non-contraceptive use (i.e. including contraceptive exposure time and exposure time of non-use of contraceptives) (Objective 1c is added as post-hoc analysis with amendment dated 28 October 2020).

7.1.2 Secondary objectives

The secondary aims of the study are:

2a. To describe potential risk factors associated with ectopic pregnancy in women of reproductive age at KPNC and KPSC, including demographic risk factors (e.g. age, race), current contraceptive use (hormonal and non-hormonal IUDs, COCs and POPs, and DMPA), infectious (e.g. STIs, Pelvic Inflammatory Disease [PID]), and reproductive (e.g. previous ectopic, endometriosis, and infertility diagnosis or treatment).

2b. To describe the temporal trend in the proportion of ectopic pregnancies that are managed surgically vs. medically.

2c. Enhanced identification of contraception type and validation of contraceptive use patterns (Objective 2c is added as post-hoc analysis with amendment dated 28 October 2020).

2d. To describe potential risk factors associated with ectopic pregnancy in women with current contraceptive use and non-contraceptive use including all observation time for the Aim 1a cohort (i.e. all potentially at-risk exposure time will be categorized as contraceptive exposure time or time of non-use of contraceptives) (Objective 2d is added as post-hoc analysis with amendment dated 28 October 2020).

8. Amendments and updates

8.1 Validation study

Case ascertainment is a critical part of this study to assess the incidence of and risk factors for ectopic pregnancy. Therefore, a well-designed validation study was necessary to strengthen our study in the current health care systems. The methodology for ectopic pregnancy case ascertainment comes primarily from a study by Scholes et al in which they developed an algorithm to improve on ectopic pregnancy case finding. We added a supplement to the current study to validate ectopic pregnancy case ascertainment using both the Scholes et al algorithm (including equivalent ICD 10 codes) and an enhanced algorithm that considers differences in the study time frame, health systems, and EHR documentation. Results of the validation study are incorporated in this final report.

8.2 Post-hoc Analyses

28 October 2020 - Post-hoc analyses aimed at 1. Contraceptive identification and validation, 2. Additional analysis to augment Aim 1b and 2a analyses, and 3. Study timeframe extension to include 2019 data

The purpose of the post-hoc analyses was to:

1. Improve the contraception identification algorithm (specifically IUD type identification)
2. Conduct a formal validation of electronic abstraction of contraceptive use patterns (Aim 2c)
3. Examine incidence of ectopic pregnancy and potential risk factors for ectopic pregnancy using all observation time for the Aim 1b cohort (i.e. contraceptive exposure time and time of non-use of contraceptives, without censoring observation time at the end of contraceptive use) with non-contraceptive use as a reference category. (Aim 1c and 2d)
4. The study timeframe was also be extended to include 2019 data.

9. Research methods

9.1 Study design

We conducted a population-based cross-sectional study and a retrospective cohort study of reproductive age women at KPNC and KPSC using data abstracted from Kaiser Permanente's EHR, regional claims systems, and administrative databases.

9.1.1 Setting

KPNC and KPSC are the two largest of Kaiser Permanente's nine regional entities in the United States. KPNC is an integrated health care system with a service area that encompasses the San Francisco Bay Area and the Central Valley of California, from the Sacramento area in the north to Fresno in the south. KPNC provides care to approximately 4.4 million racial/ethnically diverse members – over 30% of the insured population in its service area. KPNC operates 21 hospitals and over 200 outpatient clinics and utilizes an EHR based on an EPIC® platform. KPSC is the largest KP system, it also has a highly racial/ethnically diverse population of approximately 4.6 million members in Los Angeles and counties throughout Southern California. It has 15 hospitals and over 227 outpatient clinics. KPSC also utilizes an EHR based on an EPIC® platform. Both KP entities provide comprehensive care; members receive their care essentially exclusively from Kaiser Permanente physicians and allied staff in the medical centers and medical office buildings owned or operated by the health plan.

9.1.2 Representativeness

KPNC and KPSC provide health coverage for about 9 million patients, representing roughly 40% of the commercially insured patients and one quarter of the Medicare patients in the state. They are broadly representative of the population of California with the exception of extremes of income.

9.1.3 Subjects and study time frame

To estimate incidence of ectopic pregnancy (Aim 1a), women were included in the study if they were at least 15 years old and not older than 44 years and had at least 1 month of enrollment in the health plans from January 1, 2009 to December 31, 2018. Cohort members could have one or more periods of continuous enrollment. Administrative enrollment gaps of $\leq$ 93 days were allowed (considered continuous enrollment). Up to three subsequent periods of enrollment were included if a cohort member re-enrolled after a period of greater than 93 days. For aim 1b and 2a, and aim 1c and 2d to capture woman-time at risk of contraceptive use and to assess potential risk factors associated with ectopic pregnancy, the study population included women from the aim 1a cohort with at least 12 months of continuous enrollment before the study inclusion date or a subsequent enrollment period. For aim 1b and 2a, and aim 1c and 2d, women who were not at-risk for pregnancy secondary to menopause or ovarian failure (aim 1b and 2a), or bilateral oophorectomy or hysterectomy based on information from the 12-month look-back window were excluded. For the post-hoc analyses with the amendments dated 28 October 2020 the eligible enrollment and observation period was extended to December 31, 2019.

9.2 Variables

9.2.1 Outcome definition

The primary outcome, ectopic pregnancy, defined as extra-uterine pregnancy, was identified using a combination of International Classification of Diseases (ICD) diagnosis and procedure codes, Current Procedural Terminology (CPT-4) codes, and National Drug Code (NDC) and KP specific medication codes. We validated and used an enhanced version of an algorithm developed by Scholes et al. for case-finding. Cases with one or more ectopic pregnancy ICD-9 or ICD-10 diagnosis or procedure code or CPT-4 code with or without a methotrexate medication code were considered a true case based on the algorithm (Figure 2). For women who had more than one ectopic pregnancy episodes (greater than 180 days apart), each ectopic pregnancy was counted.

9.2.2 Covariate definition

Age in years during the study period was used to determine eligibility for study and age at the time of the outcome of interest, ectopic pregnancy, was calculated on the date of diagnosis. The following covariates in Table 2 were assessed.

9.2.2.1 Table 2. Covariate List

Variable	Derived	Category	Description	Comments
Database			Study Site 1=KPNC 2=KPSC	Study inclusion Aim 1a
Lookback period			Number of days before the index date assess contraception and risk factors (min 365; min 182 for sensitivity analysis)	
DOB		Demographic		Study inclusion Aim 1a
Age	X	Demographic	Six categories (15-19, 20-24, 25-29, 30-34, 35-39, 40-44) for descriptive tables. Continuous variable for Poisson and Cox regression.	
Race/Ethnicity	X	Demographic	Using race variable and Hispanic indicator: non-Hispanic white, Hispanic white, non-Hispanic black, Hispanic black other Hispanic, Asian/Pacific Islander, multiple races/ethnicities, other race/ethnicity, unknown RECODE: White, Black, Hispanic, Asian/Pacific Islander, Multi-race/ethnicity, unknown	Study inclusion Aim 1a
Socio-economic status	X	Demographic	Median family household income using census tract data 6 categories: <$30,000, 30,000-49,999, 50,000-69,999, 70,000-89,999, and >$90,000; missing	Study inclusion Aim 1a Update at the first index date for Aim 1b and 2a
Smoking status		Behavioral Risk Factor	Current smoking in the year prior to index date (Never/Former/Current/Missing) Limit to within 365 days prior to index date ICD codes and Social History data source	Time varying*
Parity		Clinical Risk Factor	Parous (Any deliveries ever) (Yes/No/Missing) 0='No' 1,2,3, etc.='Yes' 999= 'Missing'	Time varying*
Congenital malformations		Clinical Risk Factor	Uterine anomalies that might increase risk for endometriosis or ectopic pregnancy (Yes/No) Diagnostic codes	Time varying*
Cesarean section		Surgical Risk Factor	Any Caesarean Sections ever (Yes/No) Diagnostic and procedure codes	Time varying*
Ectopic pregnancy history		Clinical Risk Factor	1=History of ectopic pregnancy by dx codes 2=Ectopic pregnancy observed in the dataset using the enhanced algorithm 3=Both Diagnostic and procedure codes	Time varying*
Pelvic Inflammatory disease history	X	Clinical Risk Factor	Acute inflammation of the adnexal structures or pelvis PID_2more = 2 or more PID dx codes within 30 days	Time varying*

Variable	Derived	Category	Description	Comments
Chlamydia or Gonorrhea		Clinical Risk Factor	Sexually transmitted infection (Yes/No) Laboratory test positive and/or Diagnostic codes	Time varying*
Endometriosis		Clinical Risk Factor	Pelvic endometriosis – extrauterine endometrial tissue (Yes/No) Diagnostic codes	Time varying*
Infertility diagnosis		Clinical Risk Factor	Inability or difficulty conceiving spontaneously without medical intervention (Yes/No) Diagnostic codes	Time varying*
Appendicitis/ Appendectomy		Surgical risk factor	History of Appendicitis or surgery to remove the appendix; (Yes/No) Diagnostic and procedure codes	Time varying*
Tubal Ligation & Intrauterine Tubal Occlusion/ Implant		Surgical risk factor	1=Tubal ligation (laparoscopically or open)* 2= Intrauterine tubal occlusion/implant not limited to Essure (may include silicone matrix [Adiana device], essure, and others) *Indicators for both procedure codes included	Time varying*
Myomectomy		OB Surgical risk factor	Myomectomy (Yes/No) Diagnostic and procedure codes	Time varying*
Uterine Surgery		OB Surgical risk factor	Uterine surgery (Yes/No) Diagnostic codes	Time varying*
Adnexal surgery		Surgical risk factor	Surgery of or near the adnexa that might cause scarring and increase risk for ectopic (i.e. salpingostomy for ectopic pregnancy, cystectomy, salpingo-plasty, unilateral oophorectomy) (Yes/No) Procedure codes	Time varying*
Sterilization		Exclusion or Censor	Bilateral Salpingectomy Type not specified Indicators for both Procedure codes	Time varying*
Bilateral Oophorectomy		Exclusion or Censor	Removal of both ovaries (Yes/No) Procedure codes	Time varying*
Hysterectomy		Exclusion or Censor	Removal of the uterus (Yes/No) Procedure codes	Time varying*
Ovarian Failure or (premature) menopause (Aim 1b and 2a only)		Exclusion or Censor	Loss of ovarian function (Yes/No) Diagnostic codes	Time varying*
IUD Type	X	Exposure	1=hormonal 2=copper 3=unknown	
OCP type	X	Exposure	1=combined hormonal 2= progestin-only	
Combined Hormonal Contraceptive (CHC)	X	Exposure	COC = Patch = Ring	

* Time varying means all diagnostic and procedure codes were pulled during the lookback and follow-up period(s) to determine status at the specified time (i.e. at index or updated during follow-up)

9.3 Data sources

We utilized two separate EHR data sources from the two study sites for this study. KPNC and KPSC computerized health databases contain health plan enrollment information, inpatient and outpatient clinical visits, external claims and pharmacy records. The inpatient database captures all inpatient hospitalization visits, recording admission and discharge dates as well as up to ten ICD-9/10 discharge diagnoses and procedures and up to ten CPT codes. The outpatient database captures all primary care outpatient clinic visits, urgent care visits, and ER visits recording ICD-9/10 diagnoses and procedures as well as CPT-4 codes. The external claims database captures all outpatient (clinic, urgent care, and ER) and inpatient visits by KP enrollees to non-KP facilities where KP is financially responsible for the care. The pharmacy database captures medications dispensed to KP enrollees with a pharmacy benefit plan at KP-owned pharmacies. All databases are linked through a unique medical record number assigned to each enrollee, precluding multiple counting of the same health event for individuals across sources.

Both KPSC and KPNC access the Virtual Data Warehouse (VDW) which was created to facilitate multi-site research projects. Local variables are standardized using consistent naming, definitions, and formats. During a project, the programmer at the study site taking the lead on a study aim developed a single SAS program and shared it with the other site. The programs were executed at each site with minor modifications.

9.4 Study size

Ectopic pregnancy is a relatively uncommon event. Preliminary query of KPNC diagnosis and procedure codes for ectopic pregnancy for the study period of 2007-2016 revealed 10,693 episodes of ectopic pregnancy using any ectopic pregnancy related code, of which 2,617 were associated with a surgical procedure code. Preliminary query of KPSC diagnosis and procedure codes for ectopic pregnancy for the time period of 2007-2016 revealed 10,203 episodes of ectopic pregnancy, of which 3,758 were associated with a surgical procedure code. Aim 1 for the study is descriptive; however, we estimated that over the time period there would be approximately 240,000 IUD insertions (1,725,000 Woman-years) and over 1 million OCP users (8,625,000 Woman-years). For the IUD cohort, with a total of 1,725,000 person-years, there is 83% power to detect a linear decreasing trend over the 10-year study period from an ectopic pregnancy incidence rate of 0.71/1000 person-years to 0.55/1000 person-years using a two-sided Z test with continuity correction and a significance level of 0.05.

9.5 Data transformation

See 9.2.2.1 Table 2. Covariate List

9.6 Statistical methods

9.6.1 Validation study

We assessed the diagnostic validity of a previously validated algorithm by Scholes et al (Figure 1) and an enhanced version of the algorithm (Figure 2) against the gold-standard “true case” as determined by chart review.[15] The enhanced algorithm was developed through several iterative steps. First we incorporated corresponding ICD-10 diagnostic and procedure codes which were not in use when the Scholes et al algorithm was developed in 2011. We then chart reviewed an initial random sample of 100 cases (50 KPNC and 50 KPSC) which had at least one ectopic pregnancy

diagnostic or procedure code but were not classified as ectopic pregnancy by the Scholes et al. algorithm to understand the reasons for misclassifications. This information was used to modify the Scholes et al algorithm to include or exclude codes that might improve the accuracy of case ascertainment. Additionally, we performed chart review on potential ectopic pregnancy cases with an isolated ectopic pregnancy diagnostic or procedure code from telephone appointment visits (18 KPSC and 30 KPNC – up to 30 cases total if available) or outside claims encounters (11 KPSC and 22 KPNC) to assess whether these encounter types, which were not commonly used encounter types when the Scholes et al algorithm was developed, should be included in the final enhanced algorithm.

The enhanced algorithm (Figure 2) that was developed required either: 1) two or more encounters, with at least one in-person visit, with either an ectopic pregnancy code other than abdominal ectopic pregnancy (abdominal codes O00.00 and O00.01) or evidence of methotrexate use; or 2) two or more TAVs with an ectopic pregnancy code and evidence of methotrexate use; or 3) one outpatient or inpatient visit or outside claims visit with the specific ICD-9 or ICD-10 diagnostic codes 633.10, 633.11, O00.10, or O00.11; or 4) a combination of any single encounter (outpatient or inpatient visit, outside claims visit, or TAV) with an ectopic pregnancy code plus evidence of methotrexate use; or 5) a single non-TAV encounter with both an ectopic pregnancy dx and px code on the same encounter. Multiple visits with ectopic pregnancy codes occurring within a 180-day period were considered part of the same pregnancy episode, with the diagnosis date defined as the date of the first ectopic pregnancy code encountered in an episode.

9.6.1.1 Figure 1. Scholes et al. Algorithm for Identifying Ectopic Pregnancies[15]

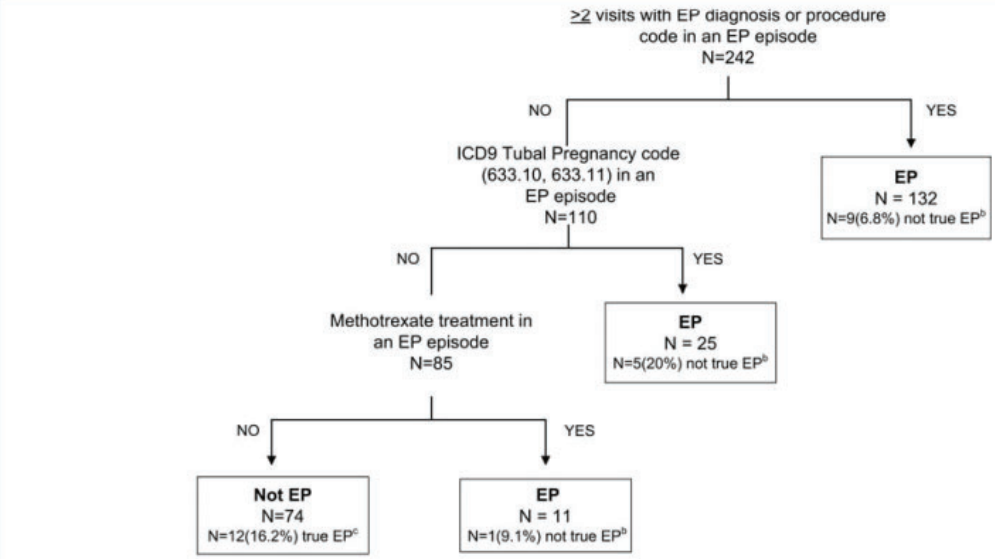


Figure 1 Algorithm for identifying ectopic pregnancy cases, Group Health development set.
EP, ectopic pregnancy; EP episode, the 180-day interval following the first date with an EP code. (a) In addition to the three predictors that comprise the final algorithm, other potential predictors that were evaluated and were not incorporated into the final model included: year of diagnosis; age at diagnosis; the occurrence of each individual EP diagnosis or procedure code; a normal intrauterine pregnancy diagnosis and/or procedure code after the EP index date; any spontaneous abortion diagnosis and/or procedure code after the EP index date; any ovarian cyst code after the EP index date; any other non-EP diagnosis code occurring on any EP diagnosis date in an EP episode; any inpatient visit during an EP episode; any ultrasound performed during an EP episode; any pelvic/transvaginal ultrasound or obstetrical ultrasound performed during an EP episode; any pelvic computerized tomography or magnetic resonance imaging performed during an EP episode; number of pregnancy tests in an EP episode; any positive pregnancy test in an EP episode; number of hCG tests in an EP episode. (b) In boxes with EP, 'N (%) not true EP' refers to cases that were misclassified by the algorithm as EP when they were not true EP. (c) In the Not EP box, 'N (%) true EP' refers to cases that were misclassified by the algorithm as not EP when they were true EP.

9.6.1.2 Figure 2. Enhanced Algorithm for Identifying Ectopic Pregnancies

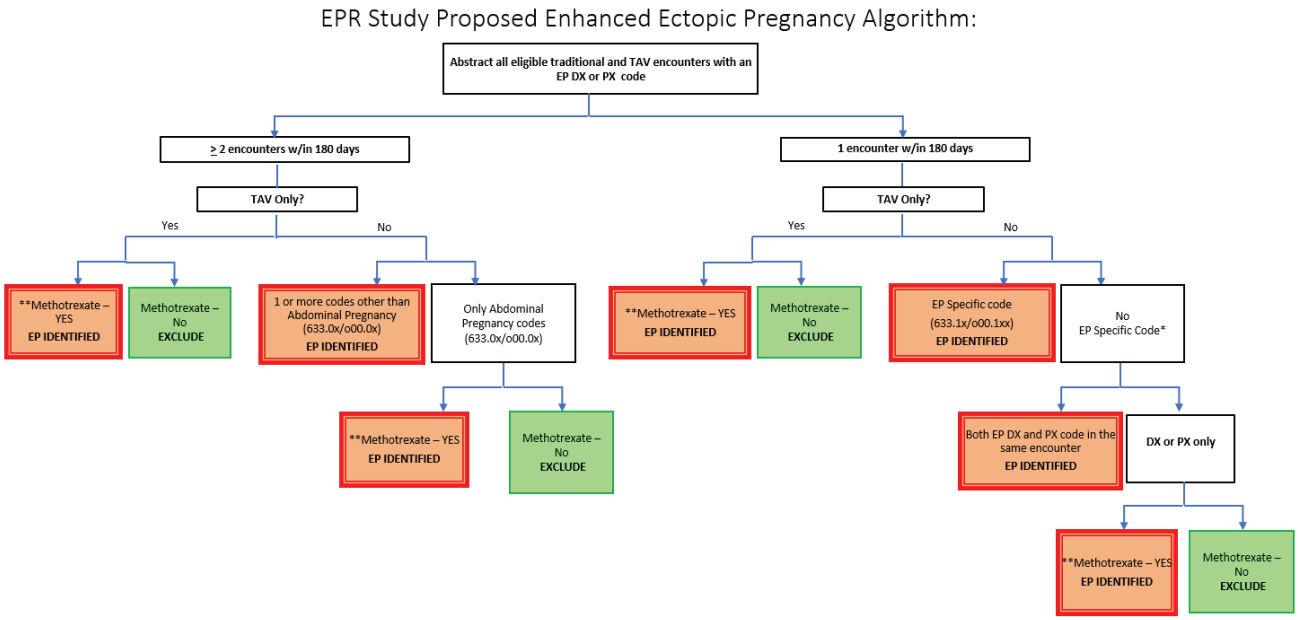


Figure 2. Legend
Abbreviations: EP, ectopic pregnancy; DX, diagnosis; PX, Procedural; TAV, Telephone Appointment Visit
*No EP-specific code, are related diagnostic and procedural codes other than 633.1x/o00.1xx
** MTX medication orders identified up to 30 days prior and 180 days after the first ectopic pregnancy diagnosis date (up to 7 days allowed in Scholes et al. algorithm)
TAV: In a telephone appointment visit, the patient speaks directly with a provider from the comfort of his/her own home or convenient location. This appointment usually lasts about 20 minutes and does not require a copay.

9.6.1.3 Validation of the algorithm

For the validation study, a random sample of 600 patients (300 at each site) with a potential ectopic pregnancy were selected. A potential case was defined as all cases with at least one ICD-9, ICD-10, or Current Procedural Technology (CPT-4) codes for ectopic pregnancy. Inclusion criteria were applied (women who were aged 15 to 44 years from January 1, 2009 to December 31, 2018 and were enrolled in the health plan for at least one month over the study period) to the 600 randomly selected cases. Cases that did not meet these requirements were excluded, leaving 255 cases at KPSC and 276 at KPNC. We randomly selected 250 cases from each site for this validation study for chart review.

Diagnostic and procedures codes were captured from the inpatient, outpatient and external claims databases. Multiple encounters with ectopic pregnancy codes within a 180-day period were considered part of the same episode. The episode date was defined as the first visit date with relevant diagnosis/procedure codes in the 180-day episode window.

Using a standardized abstraction form, chart reviews were performed by trained abstractors to identify true ectopic pregnancy cases. Cases where ectopic pregnancy status was unclear were identified and adjudicated by a clinician. Information on treatment modality (surgical vs. medical) was also collected. Ectopic pregnancy cases were classified as surgically managed if the patient had undergone any ectopic pregnancy removal surgery within 180 days of the first encounter with an ectopic pregnancy code, regardless of whether the patient received methotrexate. Remaining ectopic pregnancy cases were classified as medically treated if the patient received Methotrexate for an ectopic pregnancy. Cases for which the type of treatment could not be determined were considered unclassified.

We summarized the performance of both algorithms by site calculating:

- Sensitivity - percentage of chart review-confirmed cases that were correctly classified as ectopic pregnancy by the algorithm
- Specificity - percentage of cases determined not to be ectopic pregnancy by chart review that were correctly classified by the algorithm
- Positive Predictive Value (PPV) - percentage of cases classified as ectopic pregnancy by the algorithm that were chart review confirmed cases
- Negative Predictive Value (NPV) - percentage of identified cases classified as not ectopic pregnancy by the algorithm that were determined not to be ectopic pregnancy cases from chart review
- Youden's J statistic (Youden's index): to compute the performance of a dichotomous diagnostic test. Youden's Index: Sensitivity + Specificity – 1
- F-score (the weighted harmonic mean of the test's precision and recall): 2 x (PPV x Sensitivity) / (PPV + Sensitivity)

In addition, we evaluated the performance of electronic abstraction to correctly identify as well as overall accuracy of ectopic pregnancy management type(medical or surgical) among confirmed ectopic pregnancy cases (by both algorithm and chart review) compared to chart review using the same performance measures as well as overall accuracy.

9.6.1.4 Sensitivity Analysis

We conducted a sensitivity analysis calculating the same performance measures for the Scholes et al. and the enhanced algorithm for the subset of cases from 2009 to the end of 2014 (ICD-9 only cases)

9.6.2 Aim 1a and 2b

For Aim 1a, ectopic pregnancy rates were calculated based on two denominators: (1) woman-years or the length of enrollment among women of reproductive age (15–44 years) during the study period, and (2) number of pregnancies in this group of women during the same study period. We included live births, ectopic pregnancies, and induced abortions in the second denominator. Both denominators were stratified by 1–calendar year groups and 5-year age groups. Rates per 10,000 woman-years and per 1,000 pregnancies were calculated as the number of ectopic pregnancy cases divided by the total woman-years and the total number of pregnancies, respectively. We assessed for changes in the age distribution of KP enrollees over the 10-year study period and calculated age-adjusted rates per 10,000 woman-years, standardized to the KPNC and KPSC population

distributions at the mid-point in 2013 for the first denominator and standardized to the KPNC and KPSC pregnant population in 2013 for the second denominator. Poisson regression models adjusting for overdispersion, with calendar-year fitted as a continuous variable were used to evaluate any linear trends in rates over the study period between 2009 and 2018.

For aim 2b, the secondary outcome, surgical treatment of ectopic pregnancies, was addressed. Ectopic pregnancies were categorized to the degree possible as surgical treatment or ectopic pregnancies treated with methotrexate. Cases treated medically with methotrexate and surgically were categorized as surgical treatment. Cases for which treatment type could not be determined (including expectant management) were classified as unknown/other. The proportion of cases with surgical treatment each year over the study period was calculated and the trend was evaluated using the Cochran-Armitage test for a linear trend in proportions.

9.6.3 Aim 1b

For aim 1b, Contraceptive start and stop dates for the contraceptives of interest were identified over time; women may have had one or more periods of IUD, OCP and DMPA use as well as concurrent use or two methods. The index date was defined as the first date in an enrollment period when the eligibility criteria was met (at least 12 months of prior health plan membership). A second or third subsequent index date was created for women with more than one enrollment period. Use of hormonal contraception was updated every 90 days throughout the follow-up period, and the status of women changed when they stopped or changed the type of hormonal contraception used. Contraceptive stop dates were imputed at the end of an enrollment period, or if a contraceptive implant insertion, ectopic pregnancy, livebirth, or induced abortion was identified before a stop date. Total woman-years of IUD, OCP and DMPA exposure were calculated. Women were censored at the time of diagnosis of menopause or ovarian failure, or bilateral oophorectomy or hysterectomy procedure. Women were temporarily censored during pregnancy gestations that ended in a live birth (based on gestational days), or induced abortion (60 days), and after an ectopic pregnancy diagnosis, live birth, or induced abortion (30 days).

Ectopic pregnancy incidence rates and trends were calculated for levonorgestrel and copper IUDs, COCs and POPs, and DMPA use. An ectopic pregnancy was considered to have occurred during method use if the ectopic pregnancy diagnosis date occurred one day after a IUD or DMPA start date and up to 42 days after the stop date. For OCPS, an ectopic pregnancy was considered to have occurred during method use if the ectopic pregnancy diagnosis date occurred on the start date and up to 42 days after the stop date. We assigned one method of contraceptive use at any given time using an algorithm which prioritized: 1) an IUD or DMPA start during OCP use; 2) a DMPA start during IUD use; 3) IUD start during DMPA use; 4) a second type (POP or COC) of OCP start during a first type of OCP use. When there was method overlap (1- 4 above) we imputed a stop date for the non-prioritized method. If an OCP start and stop date fell within the start and stop dates of DMPA or IUD use, OCP use was not assigned during that time. If OCP use continued beyond the DMPA or IUD stop date, a new OCP start date was imputed. Incidence rates were expressed per 10,000 woman-years of contraceptive method exposure. Poisson regression models adjusting for overdispersion, with calendar-year fitted as a continuous variable were used to evaluate any linear trends in rates over the study period between 2009 and 2018.

9.6.4 Aim 2a

For aim 2a, the study population was followed until the diagnosis of ectopic pregnancy, end of health plan enrollment, age ≥45 years, or the end of follow-up on December 31, 2018. Women were

also censored at the time of diagnosis of menopause or ovarian failure, or bilateral oophorectomy or hysterectomy surgical procedure. Multivariable Cox proportional hazards modeling was used to model ectopic pregnancy as a time to event outcome, allowing for multiple ectopic pregnancy events, interval censoring, time-varying covariates and accounting for correlation within women contributing multiple time intervals of observation. Follow-up began at the index date, as described above. Contraceptive exposure was calculated similarly to aim 1b, for IUD, COC, POP, and DMPA use and treated as a time-varying covariate. OCP exposure time that overlapped with IUD exposure time was considered as IUD exposure time only. Crude woman-year rates intervals were calculated for each contraceptive method use. Hazard ratios (HR) and 95% confidence intervals (CI) for risk of ectopic pregnancy were estimated for levels of the risk factor in comparison to a chosen reference level (e.g. hazard ratios for smoking status would compare the incidence rates of ectopic pregnancy among those who ever smoked to those who never smoked). We used a Wald test to determine whether each risk factor had a statistically significant association with ectopic pregnancy. Simple adjusted models controlling for age, calendar year, site and hormonal contraceptive use and fully adjusted models including relevant risk factors were developed.

9.6.5 Aim 2c (Post-hoc analysis)

The contraceptive algorithm developed for Aim 1b and 2a was refined in a series of iterative steps that included used of NLP of clinic notes to identify IUD type for IUDs inserted before enrollment start. We then assessed the diagnostic validity of the contraceptive algorithm against the gold-standard "true case" as determined by chart review. Condom use and other methods not considered methods of interest (e.g. natural family planning or sterilization) were considered as contraceptive non-use. Charts were reviewed by trained research staff who used a standardized form to capture data. Up to 5 algorithm-based periods of method use or the entire enrollment period for women who used no methods were reviewed. Cases where contraceptive use status was unclear was identified and adjudicated by an expert clinician on an ongoing basis. Cases with insufficient information to determine contraceptive use status were excluded. Positive predictive value (PPV), the percentage of contraceptive use periods determined by the algorithm that were confirmed by chart review among all contraceptive use periods with 95% confidence interval (CI), were calculated overall, by each method of interest (hormonal, non-hormonal and unknown type of IUDs, COCs and POPs, DMPA, transdermal patches, vaginal rings, and implants) and for women with no contraceptive method use. Transdermal patches, and vaginal rings were analyzed as a group.

9.6.6 Aim 1c (Post-hoc analysis)

For Aim 1c and 2d, we also considered person-time during use of implants, transdermal patches, and rings, and when the contraceptive method of interests were not used (non-use observation time). Transdermal Patch and Ring exposure time was handled like OCP exposure time and was based on number of packs dispensed in the pharmacy databases using relevant medication codes. One ring or 1 box (4 patches) will be assumed to be 28 days). Implant start date was based on evidence of insertion procedure and medication codes. End dates were based on evidence of removal diagnosis and procedure codes, evidence of insertion of a subsequent IUD or implant, or subsequent DMPA injection, livebirth, or induced abortion. Since women may have had an implant inserted prior to enrollment at KPNC or KPSC, data on implant use was also augmented using surveillance codes. Periods of time with no prescription contraceptive use were grouped into two categories: no use or no use following discontinuation of prescription contraceptive use in the last 12 months.

Ectopic pregnancy incidence rates and temporal trends were calculated for each contraceptive method of interest (hormonal, non-hormonal and unknown type of IUDs, COCs and POPs, DMPA, transdermal patches, vaginal rings, and implants) similar to Aim 1b; however, for this aim we also estimated observation time when women did not use one of the study methods of interest. COC, transdermal patches, and vaginal rings were handled the same (COC=patch=ring) and analyzed as a group. An ectopic pregnancy was considered to have occurred during method use if the ectopic pregnancy diagnosis date occurred 14 days after a method start date and up to 42 days after a stop date. We assigned one method of contraceptive use at any given time using an algorithm which prioritized: 1) an IUD, Implant, or DMPA start during pill, patch, or ring use; 2) a DMPA start during any other method use; 3) IUD or Implant start during DMPA use; 4) a POP or COC start during POP or COC use. When there was method overlap (1- 4 above) we imputed a stop date for the non-prioritized method. If an OCP start and stop date fell within the start and stop dates of DMPA, IUD, or implant use, OCP use was not assigned during that time. If OCP use continued beyond the DMPA, IUD, or implant stop date, a new OCP start date was imputed. Incidence rates are expressed per 10,000 woman-years with 95% confidence intervals of contraceptive method exposure and exposure time when no methods of interest are used.

9.6.7 Aim 2d (Post-hoc analysis)

This analysis was similar to that of Specific Aim 2a, but included the exposure of patches, rings, and implants and non-contraceptive use. Eligible women were aged 15 to 44 years between January 1, 2010 and December 31, 2019 with at least 12 months of continuous enrollment (no more than a 93-day gap) before the study inclusion date were included. Women were excluded if they had a history of hysterectomy or bilateral salpingo-oophorectomy or oophorectomy. Since women used multiple methods and have periods of non-use, descriptive analysis of relevant variables was based on the index date. The index date was defined as the first date in an enrollment period when the eligibility criteria was met. Non-contraceptive use following discontinuation of prescription contraceptive use in the last 12 months was the comparator when examining ectopic pregnancy (EP) risk by method type.

The distribution of cohort characteristics by earliest contraceptive method use status were compared using t-tests for continuous variables and chi-square tests for discrete variables. Women were censored at the time of diagnosis of menopause or ovarian failure, or bilateral oophorectomy or hysterectomy surgical procedure as well as disenrollment/mortality or end of study. We included up to 3 enrollments from the same member as long as the inclusion/exclusion criteria mentioned above were met.

Multivariable Cox proportional hazards modeling was used to model EP as a time-to-event outcome, allowing for multiple EP events, time-varying covariates and accounting for correlation within women contributing multiple time intervals of observation. Crude woman-year rates intervals were calculated for each contraceptive method used. Hazard ratios (HR) and 95% confidence intervals (CI) for risk of EP were estimated for levels of the risk factor in comparison to a reference level that was chosen *a priori*. Fully adjusted models including potential risk factors, if they resulted in p-value <.05 from the crude analysis, and clinically important risk factors were developed.

The completeness of data on self-reported smoking status is questionable. Since excluding missing information on smoking status may result in an incorrect estimate of its association with the risk of ectopic pregnancy, we retained missing values in all analyses.

10. Results

10.1 Participants

10.1.1 Validation Study

A random sample of 600 patients (300 at each site) with a potential ectopic pregnancy were selected from the 21,737 (10,369 KPNC, 11,368 KPSC) potential ectopic pregnancy cases for the validation study (Figure 3). Inclusion criteria were applied (aged 14-45 years with KP membership at ectopic pregnancy automated diagnosis date) to the 600 randomly selected cases. Cases that had a "Missing" or "Uncertain" ectopic pregnancy case status upon chart review were not included in the final analyses, leaving 255 cases at KPSC and 276 at KPNC. The decision was made to randomly select 250 cases from each site (rather than 300 at each site).

10.1.1.1 Figure 3. Validation Study Population

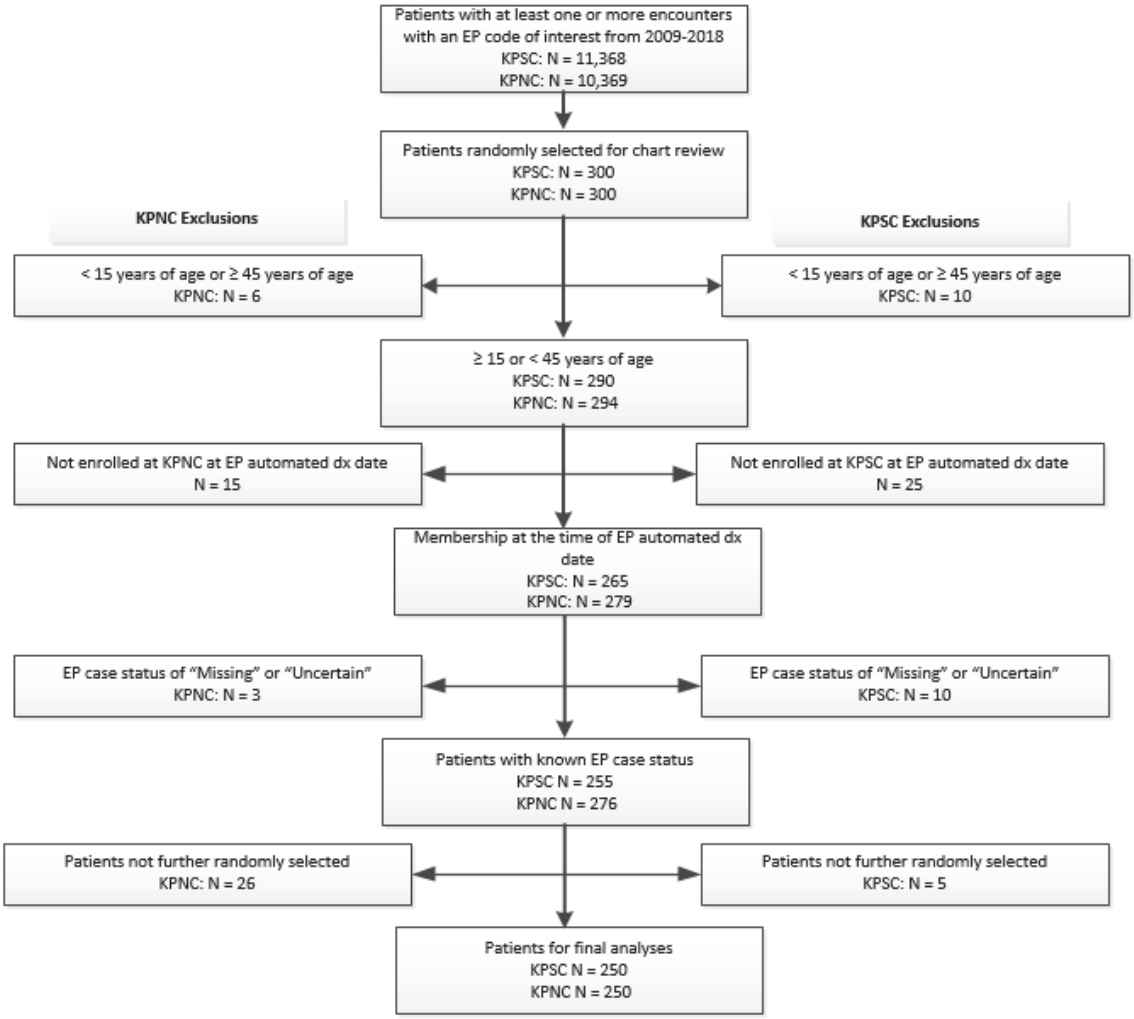


Table 3 shows the distribution of maternal characteristics among the study sample and the two study sites (KPSC and KPNC) from which the sample for this validation study was drawn. Only a small proportion of the women in the sample population were teens and over a third were Hispanic. There was a higher proportion of Hispanics at KPSC than KPNC and a higher proportion of non-Hispanic white and Asian/Pacific Islanders at KPNC than at KPSC. Only a small proportion of women in the sampled cohort lived in neighborhoods with a median annual household income below $30,000. Although, the distribution of maternal characteristics is largely comparable between the sampled population and the overall cohort, women in the sampled population were slightly more likely to be from non-Hispanic Black and less likely to be from non-Hispanic White racial/ethnic background.

10.1.1.2 Table 3 Characteristics of the validation study sample and overall population

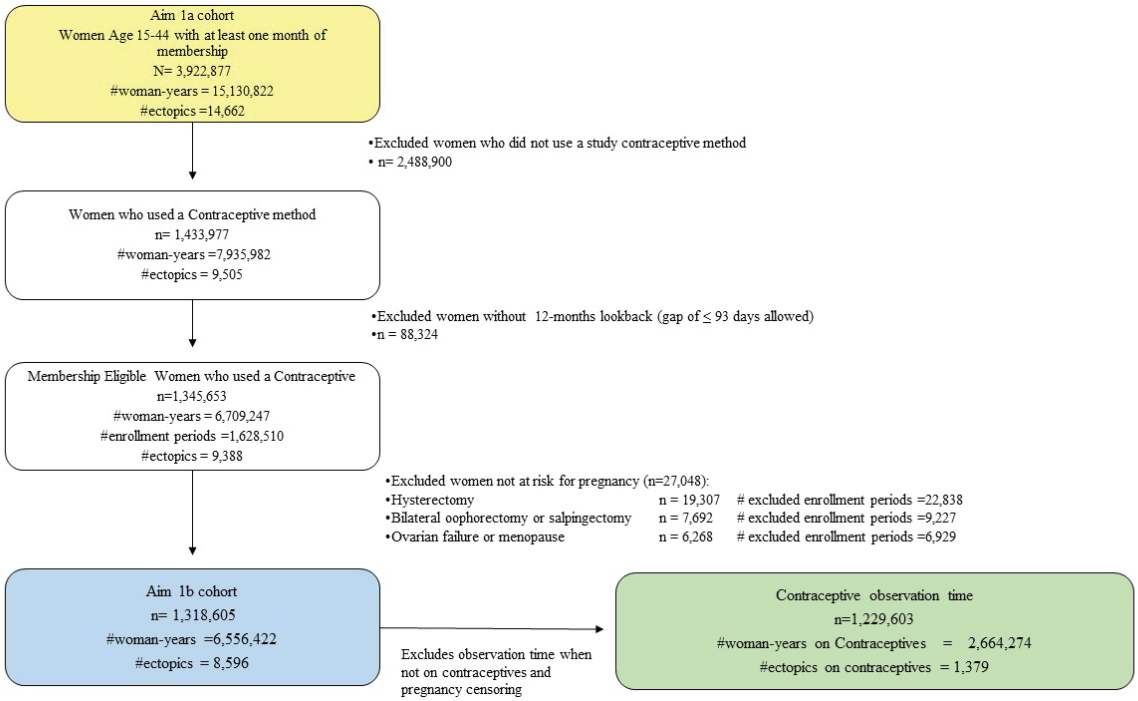
Characteristics	Sample (n=500)		Overall population		
	Chart reviewed	Column (%) in reviewed charts	Total N=19,615 (%)	KPSC N=9,823 (%)	KPNC N=9,792 (%)
Maternal age, years					
<20	22	4.4	668 (3.4)	353 (3.6)	315 (3.2)
20-29	169	33.8	7,036 (35.9)	3,643 (37.1)	3,393 (34.7)
30-34	157	31.4	6,073 (31.0)	2,970 (30.2)	3,103 (31.7)
≥35	152	30.4	5,838 (29.8)	2,857 (29.1)	2,981 (30.4)
Race/ethnicity					
Non-Hispanic White	124	24.8	5,458 (27.8)	2,257 (23.0)	3,201 (32.7)
Non-Hispanic Black	82	16.4	2,579 (13.1)	1,298 (13.2)	1,281 (13.1)
Hispanic	199	39.8	7,668 (39.1)	4,960 (50.5)	2,708 (27.7)
Asian/Pacific Islander	83	16.6	3,261 (16.6)	1,069 (10.9)	2,192 (22.4)
Other	4	0.8	349 (1.8)	144 (1.5)	205 (2.1)
Unknown	8	1.6	300 (1.5)	95 (1.0)	205 (2.1)
Smoking[a]					
No	461	92.2	17,947 (91.5)	8,929 (90.9)	9,018 (92.1)
Yes	39	7.8	1,668 (8.5)	894 (9.1)	774 (7.9)
Parity					
Nullipara	146	29.2	5,690 (29.0)	2,671 (27.2)	3,019 (30.8)
Multipara	259	51.8	10,444 (53.2)	5,214 (53.1)	5,230 (53.4)
Missing/unavailable	95	19.0	3,481 (17.7)	1,938 (19.7)	1,543 (15.8)
Income[b] (Dollars)					
< $30,000	31	6.2	1,092 (5.6)	584 (6.0)	508 (5.2)
$30,000-$49,999	117	23.4	4,863 (24.8)	2,806 (28.6)	2,057 (21.0)
$50,000-$69,999	147	29.4	5,474 (27.9)	2,913 (29.6)	2,561 (26.2)
$70,000-$89,999	104	20.8	4,131 (21.1)	1,969 (20.0)	2,162 (22.1)
≥ $90,000	101	20.2	4,033 (20.6)	1,535 (15.6)	2,498 (25.5)

[a]Smoking status documented within the year prior to the index date
[b]Median family household income based on census tract of residence

10.1.2 Study population

From 2009 to 2018, there were 3,922,877 women aged between 15 and 44 years, who contributed 15,130,882 woman-years of total observation time at the two study sites combined (Figure 4). Among these women, 1,433,977 had used an IUD, OCP, or DMPA at some point during the study period. After excluding women who did not meet the enrollment eligibility criteria and censoring for known periods when not at risk for pregnancy including time after menopause, ovarian failure, bilateral oophorectomy, hysterectomy or pregnancy there were 1,318,605 women who contributed 6,556,422 women-years of observation time (Aim 1b cohort). After excluding observation time when these women were not using a contraceptive method there were 1,229,603 women who contributed 2,664, 274 women-years of observation (Figure 4). Roughly half of the study papulation was from each of the study sites; the study population for KPNC and KPSC is provided separately in Annex 4 - Table iii and iv.

10.1.2.1 Figure 4. Study population



10.2 Main results

10.2.1 Validation Study

Chart review demonstrated that 334 (66.8%) of the 500 cases were true ectopic pregnancies and 166 (33.2%) were not confirmed as ectopic pregnancies. The sensitivity, specificity, PPV, and NPV of using the Scholes algorithm and the enhanced algorithm for identifying ectopic pregnancies are presented in Table 4. The sensitivity and NPV for the Scholes algorithm were lower at 94.3% and 88.1%, respectively, compared to enhanced algorithm at 97.6% and 94.6% respectively. Furthermore, the overall performance (Youden's index and F-score) of the enhanced algorithm was

higher than the performance of Sholes algorithm 82.5 and 95.2 versus 78.7 and 93.3 respectively. Data for KPNC and KPSC is provided separately in Annex 4 - Table iii and iv. Performance was similar for KPNC and KPSC.

We evaluated the performance of electronic abstraction of codes to correctly identify management in the 326 ectopic pregnancy cases identified by the enhanced algorithm. Chart review revealed that 197 (60.4%) were managed surgically, 126 (38.7%) were managed medically, and 3 (0.9%) could not be classified. Electronic abstraction of codes assigned 186 (57.1%) ectopic pregnancy cases as managed surgically, 124 (38.0%) as managed medically, and 16 (4.9%) could not be classified. Performance of electronic chart abstraction of codes to assign ectopic pregnancy management compared to chart review is provided in Table 5. The sensitivity of surgical procedure codes from electronic chart abstraction to correctly identify surgical management was 91.9%. The overall accuracy, defined as the percentage of ectopic pregnancy cases with correct management (surgical, medical, and unclassified) identified by electronic chart abstraction, was 92.3%. Data for KPNC and KPSC is provided separately in Annex 4 - Table v and vi. Performance was similar for KPNC and KPSC.

10.2.2 Table 4. Ectopic Pregnancy Ascertainment - Performance of Scholes and the enhanced ectopic pregnancy algorithms

		Scholes Algorithm			Enhanced Algorithm		
		Yes	**No**	**Total**	**Yes**	**No**	**Total**
Chart Abstraction	**Yes**	315	19	334	326	8	334
	No	26	140	166	25	141	166
	Total	341	159	500	351	149	500
Test Characteristics	**Sensitivity**	94.3			97.6		
	Specificity	84.3			84.9		
	Negative predictive value	88.1			94.6		
	Positive predictive value	92.4			92.9		
	Youden's index	78.7			82.5		
	F-score	93.3			95.2		

10.2.4 Table 5. Ectopic Pregnancy Management ascertainment – Performance of electronic data abstraction

		Enhanced Algorithm Cases*			
		Surgical	**Medical**	**Unclassified**	**Total**
Chart abstraction	**Surgical**	181	5	11	197
	Medical	5	118	3	126
	Unclassified	0	1	2	3
	Total	186	124	16	326*

		Surgical Management Enhanced Algorithm vs. Chart review
Test Characteristics	**Sensitivity**	91.9
	Specificity	96.1
	Negative predictive value	88.6
	Positive predictive value	97.3
	Youden's index	88.0
	F-score	94.5
	Overall accuracy†	92.3

* Includes cases confirmed as ectopic pregnancy by chart review and the enhanced algorithm
† The percentage of ectopic pregnancy cases with correct management (surgical, medical, and unclassified) identified by electronic chart abstraction

10.2.5 Validation Study sensitivity analysis

Sensitivity analysis limiting data to the subset of cases (n=307) from 2009 to 2014 with ICD 9 only cases revealed sensitivity and NPV were similar at 94.5% and 85.9%, respectively (Table 6), for the Scholes subset analysis compared to 94.3% and 88.1% respectively for the Scholes full dataset (Table 4). The performance of the enhanced algorithm in the subset analyses was also similar to performance of the enhanced algorithm for the full dataset.

10.2.5.1 Table 6. Sensitivity Analysis - Ectopic Pregnancy Ascertainment - Performance of Scholes and the enhanced ectopic pregnancy algorithms 2009-2014 ICD-9 only subset

		Scholes Algorithm			Enhanced Algorithm		
		Yes	**No**	**Total**	**Yes**	**No**	**Total**
Chart Abstraction	**Yes**	206	12	218	212	6	218
	No	16	73	89	16	73	89
	Total	222	85	307	228	79	307

Test Characteristics	**Sensitivity**	94.5	97.3
	Specificity	82.0	82.0
	Negative predictive value	85.9	92.4
	Positive predictive value	92.8	93.0
	Youden's index	76.5	79.3
	F-score	93.6	95.1

10.3 Aim 1a/2b

From 2009 to 2018, there were 14,662 ectopic pregnancies identified among 15,130,882 woman-years, for an overall age-adjusted incidence of 9.5 per 10, 000 woman years among women aged 15-44 years (Table 7). Though the population was fairly equally distributed across the 5-year age groups, the ectopic pregnancy incidence varied by age. It was highest for women age 25-29 and 30-34 (14.3 and 17.9 per 10,000 woman-years respectively). The incidence was lowest for adolescents at 1.5 per 10,000 woman-years. The annual age-adjusted incidence of ectopic pregnancy did not change significantly over time (P-value for linear trend = 0.90) (Figure 5). The annual age-adjusted rate ranged from a low of 9.0 per 10,000 woman years in 2009 to 10.0 per 10,000 woman-years in 2015. The linear trend of increasing incidence for women aged 35-39 years was counterbalanced by a trend of decreasing incidence for women aged 15-19 and 20-24 years (*P*value for linear trend <.0001, <.0001, and <.001 respectively) (Figure 5).

Using pregnancies (ectopic pregnancies, live births, and abortions) as the denominator, the pattern was different. The overall incidence of ectopic pregnancy was highest among women with the second lowest number of pregnancies over the study period, women age 40-44, at 23.6 per 1,000 pregnancies. Adolescents had the lowest number of pregnancies over the study period; however the incidence of ectopic pregnancy among adolescents was the lowest at 8.9 per 1,000 pregnancies (Table 7). There was a significant increase in the annual age-adjusted incidence of ectopic pregnancy from 2009 to 2018 from 14.4 to 17.1 per 1,000 pregnancies (P-value for linear trend <.0001) with an overall age-adjusted rate of 15.7 per 1,000 pregnancies (Figure 6).

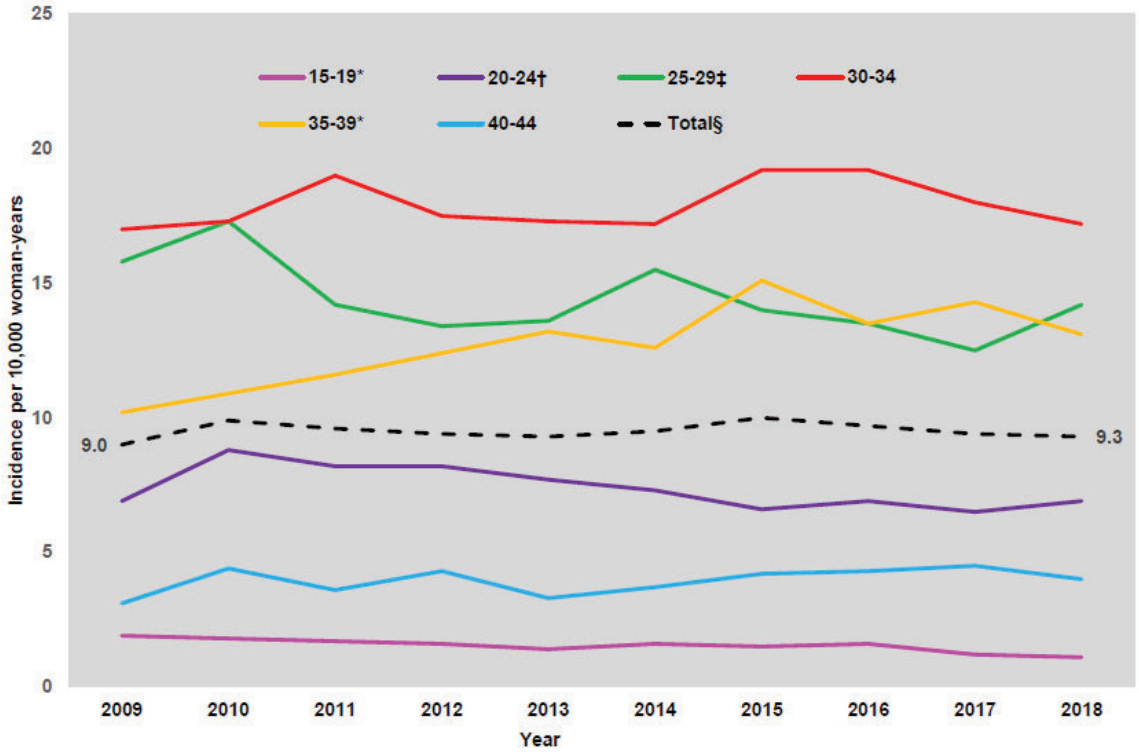
Approximately half (51.8%) of ectopic pregnancies at KPNC and KPSC were managed surgically; there was a slight increase in the proportion that were managed surgically over the 10-year study period, from 49.7% in 2009 to 53.7% in 2018, though the trend was not statistically significant (P-value for linear trends = 0.07). The incidence of ectopic pregnancy and the proportion managed surgically was similar across the two sites (Annex 4 - Table vii. and viii.).

10.3.1 Table 7. Ectopic Pregnancy Incidence 2009 - 2018

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Number of Ectopic Pregnancies											
15-19	45	44	43	40	35	40	39	41	30	29	**386**
20-24	130	165	179	191	185	184	176	191	183	200	**1,784**
25-29	323	350	302	291	298	364	367	385	381	457	**3,518**
30-34	367	380	435	415	420	439	534	567	560	565	**4,682**
35-39	232	245	263	286	309	310	400	384	434	418	**3,281**
40-44	73	103	86	105	81	93	110	118	126	116	**1,011**
All 15-44	1170	1287	1308	1328	1328	1430	1626	1686	1714	1785	**14,662**
Number of Woman-Years											
15-19	241,239	239,786	246,179	247,845	246,479	247,374	254,841	260,619	259,144	260,691	**2,504,196**
20-24	188,214	186,455	218,375	234,252	239,790	251,203	266,411	275,639	282,614	288,467	**2,431,420**
25-29	204,942	202,637	212,410	217,913	218,977	234,992	262,111	284,317	305,862	321,308	**2,465,468**
30-34	216,485	220,139	228,678	237,327	242,182	255,434	277,908	295,702	311,781	327,937	**2,613,574**
35-39	227,595	224,927	226,288	230,889	233,406	245,418	265,708	284,656	302,846	320,229	**2,561,962**
40-44	233,319	233,769	239,403	243,247	243,523	250,835	263,138	271,373	282,187	293,469	**2,554,262**
All 15-44	1,311,795	1,307,712	1,371,332	1,411,473	1,424,357	1,485,255	1,590,116	1,672,306	1,744,434	1,812,102	**15,130,882**
Ectopic Pregnancy Incidence (per 10,000 Woman Years)											
15-19	1.9	1.8	1.7	1.6	1.4	1.6	1.5	1.6	1.2	1.1	**1.5**
20-24	6.9	8.8	8.2	8.2	7.7	7.3	6.6	6.9	6.5	6.9	**7.3**
25-29	15.8	17.3	14.2	13.4	13.6	15.5	14.0	13.5	12.5	14.2	**14.3**
30-34	17.0	17.3	19.0	17.5	17.3	17.2	19.2	19.2	18.0	17.2	**17.9**
35-39	10.2	10.9	11.6	12.4	13.2	12.6	15.1	13.5	14.3	13.1	**12.8**
40-44	3.1	4.4	3.6	4.3	3.3	3.7	4.2	4.3	4.5	4.0	**4.0**
Crude	**8.9**	**9.8**	**9.5**	**9.4**	**9.3**	**9.6**	**10.2**	**10.1**	**9.8**	**9.9**	**9.7**
Age-adjusted	**9.0**	**9.9**	**9.6**	**9.4**	**9.3**	**9.5**	**10.0**	**9.7**	**9.4**	**9.3**	**9.5**
Number of pregnancies											
15-19	5,463	6,001	5,623	5,119	4,341	3,897	3,651	3,333	3,084	2,653	**43,165**
20-24	13,144	13,954	14,917	15,299	15,013	15,208	15,424	15,356	14,611	13,615	**146,541**
25-29	22,857	23,911	23,873	23,829	23,280	24,275	25,361	26,844	27,552	26,595	**248,377**
30-34	23,218	25,083	26,565	27,610	28,154	29,861	31,986	34,176	34,347	33,620	**294,620**
35-39	13,382	14,316	14,672	15,619	15,756	16,720	18,119	19,330	20,699	21,064	**169,677**
40-44	3,464	3,982	4,124	4,188	4,066	4,199	4,384	4,635	4,811	4,944	**42,797**
All 15-44	81,528	87,247	89,774	91,664	90,610	94,160	98,925	103,674	105,104	102,491	**945,177**
Ectopic pregnancy Incidence (per 1,000 Pregnancies)											
15-19	8.2	7.3	7.6	7.8	8.1	10.3	10.7	12.3	9.7	10.9	**8.9**
20-24	9.9	11.8	12.0	12.5	12.3	12.1	11.4	12.4	12.5	14.7	**12.2**
25-29	14.1	14.6	12.7	12.2	12.8	15.0	14.5	14.3	13.8	17.2	**14.2**
30-34	15.8	15.1	16.4	15.0	14.9	14.7	16.7	16.6	16.3	16.8	**15.9**
35-39	17.3	17.1	17.9	18.3	19.6	18.5	22.1	19.9	21.0	19.8	**19.3**
40-44	21.1	25.9	20.9	25.1	19.9	22.1	25.1	25.5	26.2	23.5	**23.6**
Crude	**14.4**	**14.8**	**14.6**	**14.5**	**14.7**	**15.2**	**16.4**	**16.3**	**16.3**	**17.4**	**15.5**
Age-adjusted	**14.5**	**14.9**	**14.7**	**14.6**	**14.7**	**15.1**	**16.3**	**16.1**	**16.0**	**17.1**	**15.4**
Surgical management											
Number	581	640	693	699	651	728	853	877	913	958	**7,593**
Percent (%)	**49.7**	**49.7**	**53.0**	**52.6**	**49.0**	**50.9**	**52.5**	**52.0**	**53.3**	**53.7**	**51.8**

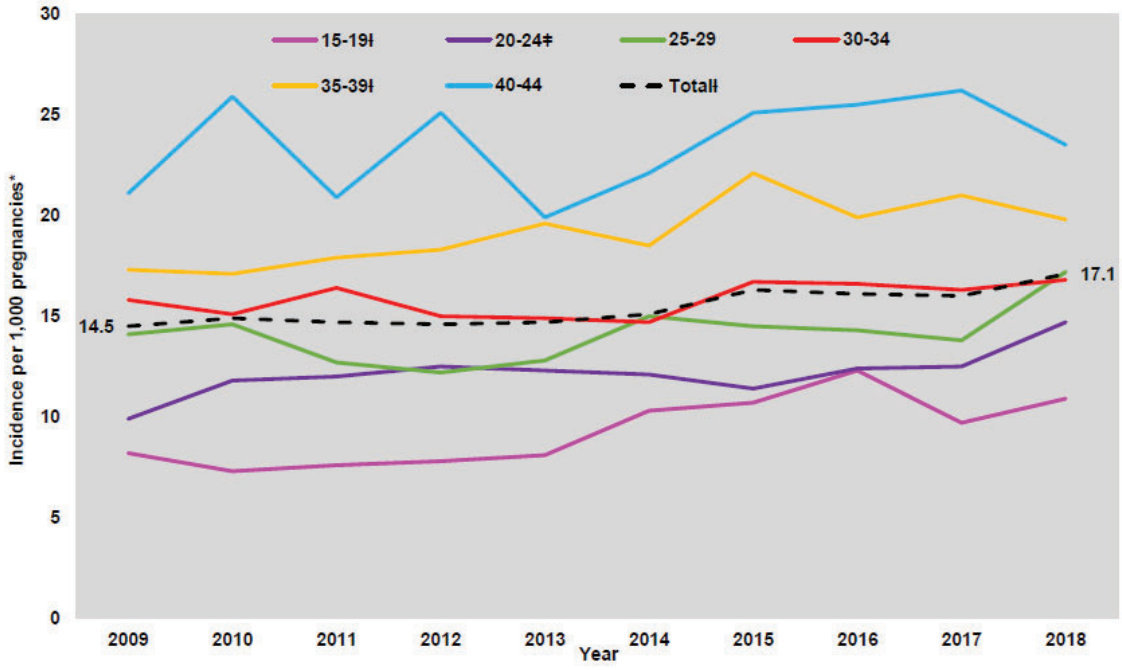
*Denominator includes ectopic pregnancies, live births, and abortions

10.3.3 Figure 5. Ectopic Pregnancy Incidence (per 10,000 woman-years) 2009 - 2018



Linear trend *Pvalue <.0001; †Pvalue <.001; ‡Pvalue 0.02; §Pvalue = 0.90

10.3.4 Figure 6. Ectopic Pregnancy Incidence (per 1,000 pregnancies) 2009 - 2018



*Denominator includes livebirths, induced abortions, and ectopic pregnancies
Linear trend †Pvalue <.0001; ‡Pvalue <.001

10.4 Aim 1b

Of the 14,662 ectopic pregnancies that were identified among women who were age 15-44 from 2009-2018 at KPNC and KPSC, 9,505 (66%) occurred in the 1,433,977 women from the study cohort who used an oral contraceptive, depot medroxyprogesterone acetate, or an IUD at some time during the study period (Figure 4). After excluding women who did not meet the 12-month health plan membership enrollment criteria and women known not to be at-risk for ectopic pregnancy, there were 8,596 ectopic pregnancies among the 1,318,605 women (Aim 1b cohort). Only 1,379 (9.4%) of ectopic pregnancies occurred in the 1,229,603 women who contributed 2,664,274 woman-years of observation time with current or recent (in the last 42 days) contraceptive use for an overall age-adjusted ectopic pregnancy incidence of 5.1 per 10,000 woman-years (Table 8).

The number of ectopic pregnancies and ectopic pregnancy incidence by current contraceptive method over the study period are presented in Table 8. The most common contraceptive method used was COCs; with 1,529,005 woman-years of observation time. Of the 1,379 ectopic pregnancies that occurred in women with current contraceptive use, 726 (53.6%) occurred with current COC use for a rate of 4.8 ectopic pregnancies per 10,000 woman-years. The incidence of ectopic pregnancy was greatest, however, among women with current POP use at 14.8 ectopic pregnancies per 10,000 woman-years of POP use. Ectopic pregnancy incidence for women with known levonorgestrel and copper IUD use was 3.4 and 6.8 per 10,000 woman-years respectively. Ectopic pregnancy incidence for women with unknown IUD type use was 8.9 per 10,000 woman-

years. Data on ectopic pregnancy incidence by current contraceptive use is presented separately for KPNC and KPNC in Annex 4 - Table ix and x.

10.4.1 Table 8. Ectopic Pregnancy Incidence by Current Contraceptive Method*, 2009–2018

	2009-2010	2011-2012	2013-2014	2015-2016	2017-2018	All 2009-2018
Number of EP by Contraceptive Method						
Combined oral contraceptive	134	124	134	148	186	**726**
Progesting-only oral contraceptive	16	25	34	40	35	**150**
Depomedroxyprogesterone acetate	10	9	11	7	4	**41**
Levonorgestrel IUD	18	47	37	42	39	**183**
Copper IUD	7	20	22	20	30	**99**
IUD Type unknown	68	45	17	31	19	**180**
All	253	270	255	288	313	**1,379**
Total Woman Years						
Combined oral contraceptive	254,840	287,784	303,379	332,499	350,503	**1,529,005**
Progesting-only oral contraceptive	13,969	16,851	20,058	24,743	25,992	**101,612**
Depomedroxyprogesterone acetate	26,129	29,591	31,663	31,691	32,129	**151,203**
Levonorgestrel IUD	42,566	91,680	117,290	133,150	151,533	**536,219**
Copper IUD	10,865	23,859	31,906	36,942	41,078	**144,649**
IUD Type unknown	54,629	39,459	36,945	38,427	32,127	**201,586**
All	402,996	489,225	541,241	597,451	633,361	**2,664,275**
EP Rate per 10,000 years of observation time						
Combined oral contraceptive	5.3	4.3	4.4	4.5	5.3	**4.7**
Progesting-only oral contraceptive	11.5	14.8	17.0	16.2	13.5	**14.8**
Depomedroxyprogesterone acetate	3.8	3.0	3.5	2.2	1.2	**2.7**
Levonorgestrel IUD	4.2	5.1	3.2	3.2	2.6	**3.4**
Copper IUD	6.4	8.4	6.9	5.4	7.3	**6.8**
IUD Type unknown	12.4	11.4	4.6	8.1	5.9	**8.9**
Overall Crude Rate	**6.3**	**5.5**	**4.7**	**4.8**	**4.9**	**5.2**
Overall Age-Adjusted Rate	**5.7**	**5.5**	**4.7**	**4.8**	**4.9**	**5.1**

*Ectopic pregnancy during current/recent contraceptive use was defined as occurring on the day of IUD/OCP start up to 42 days after IUD/OCP stop or one day after DMPA start up to 42 days after DMPA stop.

10.5 Aim 2a

Baseline demographic characteristics of the eligible women with contraceptive use during the study period are presented in Table 9. Results are presented by first method used during the study period. The most common first methods used were COCs (65.1%) and IUDs (18.8%). Across all contraceptive methods, women aged 20-29 years formed the largest group (38.4% to 44.5%) while progestin-only OCP and IUD users were more likely to be aged 30 and over (55.8% and 55.1%, respectively) compared to combined OCP and DMPA users (30.5% and 31.3%, respectively). Greater proportions of women who used DMPA were Non-Hispanic black and Hispanic (61.3% in total), where as they were only 37.9% of combined OCP users. Although there was a relatively large portion of missing information for both smoking status and parity, our data indicated that

DMPA users might be more likely to be current smokers (10.2%) compared to other methods (range 5.4% to 8.0%) and combined OCP users were more likely to be nullipara (29.9%) compared to other methods (range 15.0% to 20.3%) at first method use. DMPA users were more likely to have a neighborhood median household income below $50,000 (35.3%) compared to other methods (range 23.3% to 27.1%). Women with DMPA first method use were also less likely to have an income at or over $90,000 (15.9%) compared to other method users, with the proportions with neighborhood incomes of at or over $90,000 ranging from 24.3% to 27.4%.

Table 10 shows the incidence rates and crude and adjusted hazard ratios for ectopic pregnancy by demographic characteristics. Incidence rates for ectopic pregnancy increased with age before the age of 35 and was highest among the 30-34 year old group (7.61 per 10,000 person-years), and the association with ectopic pregnancy was 1.37-fold higher (95% CI 1.20, 1.55) for women aged 30-34 years compared to women aged 20-29 years, in the crude analysis, but this association disappeared after adjustment for factors listed in tables 10 and 11.

Non-Hispanic black women had significantly higher ectopic pregnancy incidence rates than other racial/ethnic groups. Compared to non-Hispanic white women, non-Hispanic black (adjusted HR 1.96, 95% CI 1.64, 2.35; P <0.0001) and Hispanic (adjusted HR 1.44, 95% CI 1.26, 1.64; P <0.0001) women were more likely to have a diagnosis of ectopic pregnancy. Compared to women who never smoked (incidence 5.19/10,000 person-years), current smoking was associated with increased incidence (8.96/10,000 person-years) and risk (adjusted HR 1.78, 95% CI 1.48, 2.14; P <0.0001) of ectopic pregnancy, while former smoking was not associated with ectopic pregnancy (adjusted HR 1.12, 95% CI 0.94, 1.34; P= 0.198). Incidence of ectopic pregnancy was inversely proportional to median household income, 7.95/10,000 person-years among the poorest (< $30,000) and 3.83/10,000 person-years among the wealthiest (≥ $90,000). Compared to women with the highest neighborhood income, women with income between 0- <$30,000 (adjusted HR 1.49, 95% CI 1.15, 1.93; P=0.003), $30,000-$49,999 (adjusted HR 1.21, 95% CI 1.03, 1.43; P= 0.024), and $50,000-$69,999 (adjusted HR 1.26, 95% CI 1.08, 1.47; P= 0.004) were at significantly higher risk of ectopic pregnancy.

Incidence rates and hazard ratios for the association of potential medical, obstetrical, and contraceptive risk factors with ectopic pregnancy risk are presented in Table 11. The incidence of ectopic pregnancy in women with and without a history of ectopic pregnancy were 5.08 and 42.60 per 10,000 person-years, respectively (adjusted HR 4.23, 95% CI 2.82, 6.36; P <0.0001). Among women without and with a history of STD, the incidence rates of ectopic pregnancy were 4.96 and 9.35 per 10,000 person-years, respectively (adjusted HR 1.55, 95 % CI 1.27, 1.89; P <0.0001). The incidence rates of ectopic pregnancy among women without and with PID (2 or more diagnoses) were 5.12 and 25.33 per 10,000 person-years, respectively (adjusted HR 2.87, 95 % CI 1.76, 4.67; P <0.0001), and the incidence rates of ectopic pregnancy among women without and with a history of infertility were 4.73 and 26.02 per 10,000 person-years, respectively (adjusted HR 4.79, 95 % CI 3.98, 5.77; P <0.0001). History of myomectomy (adjusted HR 2.18, 95 % CI 1.32, 3.59; P=0.002) was associated with increased risk of ectopic pregnancy; however, the risk was not increased among those women with a history of tubal ligation/occlusion or appendectomy. Although we observed significant differences in the incidence rates and increased risk in ectopic pregnancy in women with a history of cesarean delivery (crude HR 1.56, 95% CI 1.31, 1.85) and adnexal surgery (crude HR 3.11, 95% CI 2.21, 4.38) in the crude analyses, after adjusting for potential confounding variables, no significant associations were observed (adjusted HR 0.86, 95% CI 0.72, 1.03 and adjusted HR 1.21, 95% CI 0.82, 1.79, respectively).

Compared to women with current or recent DMPA use, the risk of ectopic pregnancy was significantly greater for combined OCP, progestin-only OCP and IUD users (adjusted HR 2.66, 95% CI 1.94, 3.66; 4.84, 95% CI 3.41, 6.88; and 1.99, 95% CI 1.44, 2.75; P <0.0001 respectively). Among IUD users, the risk was also elevated for women with copper IUDs and unknown IUD type (adjusted HR 2.59, 95% CI 1.80, 3.74, and 3.59, 95% CI 2.55, 5.05, P <0.0001 respectively); however there was no association between levonorgestrel IUD use and ectopic pregnancy (adjusted HR 1.25, 95% CI 0.89, 1.76; P=0.1974).

10.5.1 Table 9. Characteristics of Women with Current Contraceptive Use*

Characteristics	Contraceptive methods				†*P*-value
	Combined OCP N = 800,918 (65.1)	**Progestin-only OCP N = 90,981 (7.4)**	**DMPA N = 106,864 (8.7)**	**IUDs N = 230,840 (18.8)**	
	n(%)	n(%)	n(%)	n(%)	
Age, year					<.0001
15-19	200,190 (25.0)	3,314 (3.6)	31,128 (29.1)	15,137 (6.6)	
20-29	356,628 (44.5)	36,911 (40.6)	42,322 (39.6)	88,577 (38.4)	
30-34	116,977 (14.6)	28,632 (31.5)	15,372 (14.4)	56,270 (24.4)	
≥ 35	127,123 (15.9)	22,124 (24.3)	18,042 (16.9)	70,856 (30.7)	
Race/Ethnicity					<.0001
Non-Hispanic White	330,936 (41.3)	35,299 (38.8)	27,197 (25.5)	82,032 (35.5)	
Non-Hispanic Black	57,029 (7.1)	6,470 (7.1)	17,281 (16.2)	19,077 (8.3)	
Hispanic	246,907 (30.8)	31,180 (34.3)	48,170 (45.1)	89,047 (38.6)	
Asian/Pacific Islander	118,566 (14.8)	15,730 (17.3)	10,088 (9.4)	31,975 (13.9)	
Other/Unknown	47,480 (5.9)	2,302 (2.5)	4,128 (3.9)	8,709 (3.8)	
Smoking[a]					<.0001
Never	554,646 (69.3)	71,777 (78.9)	72,209 (67.6)	160,903 (69.7)	
Former	45,343 (5.7)	10,013 (11.0)	7,483 (7.0)	21,249 (9.2)	
Current	42,905 (5.4)	5,637 (6.2)	10,876 (10.2)	18,490 (8.0)	
Missing	158,024 (19.7)	3,554 (3.9)	16,296 (15.2)	30,198 (13.1)	
Parity					<.0001
Nullipara	239,236 (29.9)	18,474 (20.3)	20,572 (19.3)	34,677 (15.0)	
Parous	158,545 (19.8)	60,824 (66.9)	43,107 (40.3)	141,070 (61.1)	
Missing	403,137 (50.3)	11,683 (12.8)	43,185 (40.4)	55,093 (23.9)	
Median household income[b], USD					<.0001
< $30,000	29,433 (3.7)	3,250 (3.6)	7,044 (6.6)	10,604 (4.6)	
$30,000-$49,999	157,260 (19.6)	18,283 (20.1)	30,652 (28.7)	51,966 (22.5)	
$50,000-$69,999	213,491 (26.7)	24,362 (26.8)	31,465 (29.4)	62,775 (27.2)	
$70,000-$89,999	179,776 (22.4)	20,416 (22.4)	20,609 (19.3)	49,142 (21.3)	
≥ $90,000	219,694 (27.4)	24,544 (27)	16,994 (15.9)	56,121 (24.3)	
Missing	1,264 (0.2)	126 (0.1)	100 (0.1)	232 (0.1)	

*Based on first method used during the study period
Abbreviations: OCP, Oral Contraceptive Pills; DMPA, Depomedroxyprogesterone acetate; USD, United States Dollar; IUD, levonorgestrel or copper IUD
†P-values for characteristic-specific differences in contraceptive method use.
[a] Smoking status documented within year prior to the index date.
[b]Median family household income based on census tract of residence

10.5.2 Table 10. Incidence Rates per 10,000 woman-years and Risk of Ectopic Pregnancy (crude and adjusted hazard ratios) Associated with Demographic Characteristics

Characteristics	Total Woman-years	EP (N)	Incidence Rate[a]	Hazard Ratio (95% Confidence Intervals)		*P*-value
				Crude	Adjusted[b]	
Total	2,664,275	1,379	5.18	--	--	--
Age, year						
15-19	289,233	59	2.04	0.36 (0.27, 0.47)	0.50 (0.38, 0.66)	< 0.0001
20-29	1,063,957	596	5.60	1.00 (reference)	1.00 (reference)	
30-34	533,565	406	7.61	1.37 (1.20, 1.55)	0.99 (0.87, 1.14)	0.9159
≥ 35	777,520	318	4.09	0.75 (0.65, 0.86)	0.51 (0.44, 0.60)	< 0.0001
Race/Ethnicity						
Non-Hispanic White	1,145,540	449	3.92	1.00 (reference)	1.00 (reference)	
Non-Hispanic Black	197,700	181	9.16	2.35 (1.98, 2.80)	1.96 (1.64, 2.35)	< 0.0001
Hispanic	840,743	570	6.78	1.74 (1.54, 1.97)	1.44 (1.26, 1.64)	< 0.0001
Asian/Pacific Islander	382,754	152	3.97	1.02 (0.85, 1.22)	0.93 (0.78, 1.12)	0.4687
Other/Unknown	97,536	27	2.77	0.69 (0.47, 1.01)	0.74 (0.50, 1.09)	0.1239
Smoking Status[c]						
Never	1,866,156	968	5.19	1.00 (reference)	1.00 (reference)	
Former	229,847	141	6.13	1.19 (1.00, 1.42)	1.12 (0.94, 1.34)	0.1976
Current	148,478	133	8.96	1.71 (1.43, 2.05)	1.78 (1.48, 2.14)	< 0.0001
Missing	419,794	137	3.26	0.63 (0.52, 0.75)	0.75 (0.63, 0.90)	0.0020
Parity						
Nullipara	874,476	320	3.66	1.00 (reference)	1.00 (reference)	
Parous	1,186,909	870	7.33	2.03 (1.79, 2.31)	2.21 (1.90, 2.57)	< 0.0001
Missing	602,890	189	3.13	0.81 (0.68, 0.97)	0.96 (0.80, 1.16)	0.7037
Median household income[d], USD						
< $30,000	95,557	76	7.95	2.07 (1.61, 2.67)	1.49 (1.15, 1.93)	0.0026
$30,000-$49,999	513,835	315	6.13	1.60 (1.36, 1.88)	1.21 (1.03, 1.43)	0.0240
$50,000-$69,999	709,475	408	5.75	1.50 (1.29, 1.75)	1.26 (1.08, 1.47)	0.0039
$70,000-$89,999	601,173	295	4.91	1.28 (1.09, 1.51)	1.15 (0.98, 1.36)	0.0935
≥ $90,000	742,123	284	3.83	1.00 (reference)	1.00 (reference)	
Missing	2,113	1	4.73	1.18 (0.17, 8.41)	1.29 (0.18, 9.17)	0.8019

Abbreviations: EP, ectopic pregnancy; USD, United States Dollar
[a]Incidence rate is shown per 10,000 Woman-years.
[b]Hazard ratios were adjusted for covariates listed in this table and that of Table 11
[c] Smoking status documented in the year prior t the index date
[d]Median family household income based on census tract of residence

10.5.3 Table 11. Incidence Rates per 10,000 woman-years and Risk of Ectopic Pregnancy (crude and adjusted hazard ratios) associated with potential medical, obstetrical, and contraceptive risk factors

Potential risk factors	Total Woman-years	Ectopic Pregnancies (N)	Incidence[a]	Hazard Ratio (95% Confidence Intervals)		*P*-value
				Crude	Adjusted[b]	
History of ectopic pregnancy						
No	2,657,467	1,350	5.08	1.00 (ref.)	1.00 (ref.)	
Yes	6,808	29	42.60	8.73 (6.04, 12.63)	4.23 (2.82, 6.36)	<0.0001
History of STD						
No	2,534,832	1,258	4.96	1.00 (ref.)	1.00 (ref.)	
Yes	129,443	121	9.35	1.96 (1.62, 2.36)	1.55 (1.27, 1.89)	< 0.0001
History of PID (2 or more diagnoses)						
No	2,657,564	1,362	5.12	1.00 (ref.)	1.00 (ref.)	
Yes	6,710	17	25.33	5.09 (3.15, 8.21)	2.87 (1.76, 4.67)	< 0.0001
History of infertility						
No	2,608,925	1,235	4.73	1.00 (ref.)	1.00 (ref.)	
Yes	55,350	144	26.02	5.84 (4.90, 6.95)	4.79 (3.98, 5.77)	< 0.0001
History of endometriosis						
No	2,540,291	1,298	5.11	1.00 (ref.)	1.00 (ref.)	
Yes	123,984	81	6.53	1.31 (1.05, 1.64)	0.94 (0.74, 1.19)	0.5969
History of uterine malformation						
No	2,657,236	1,374	5.17	1.00 (ref.)	1.00 (ref.)	
Yes	7,039	5	7.10	1.40 (0.58, 3.38)	0.70 (0.29, 1.70)	0.4337
History of pelvic organ surgeries						
Cesarean section						
No	2,471,726	1,234	4.99	1.00 (ref.)	1.00 (ref.)	
Yes	192,549	145	7.53	1.56 (1.31, 1.85)	0.86 (0.72, 1.03)	0.1021
Tubal ligation/occlusion						
No	2,651,028	1,373	5.18	1.00 (ref.)	1.00 (ref.)	
Yes	13,246	6	4.53	0.91 (0.41, 2.02)	0.64 (0.28, 1.43)	0.2751
Myomectomy						
No	2,654,962	1,362	5.13	1.00 (ref.)	1.00 (ref.)	
Yes	9,313	17	18.25	3.67 (2.27, 5.93)	2.18 (1.32, 3.59)	0.0024
Adnexal surgery						
No	2,642,113	1,345	5.09	1.00 (ref.)	1.00 (ref.)	
Yes	22,162	34	15.34	3.11 (2.21, 4.38)	1.21 (0.82, 1.79)	0.3417
Appendectomy						
No	2,637,860	1,364	5.17	1.00 (ref.)	1.00 (ref.)	
Yes	26,415	15	5.68	1.13 (0.68, 1.88)	1.04 (0.62, 1.73)	0.8950
Any pelvic surgery						
No	2,417,941	1,174	4.86	1.00 (ref.)	1.00 (ref.)	
Yes	246,334	205	8.32	1.78 (1.53, 2.07)	1.01 (0.86, 1.19)	0.8922

Table 11 continued. Incidence Rates per 10,000 woman-years and Risk of Ectopic Pregnancy (crude and adjusted hazard ratios) associated with potential medical, obstetrical, and contraceptive risk factors

Potential risk factors	Total Woman-years	Ectopic Pregnancies (N)	Incidence[a]	Hazard Ratio (95% Confidence Intervals)		*P*-value
				Crude	Adjusted[b]	
Contraceptive method						
DMPA	151,203	41	2.71	1.00 (Ref.)	1.00 (Ref.)	
Combined OCP use	1,529,005	726	4.75	1.74 (1.27, 2.39)	2.66 (1.94, 3.66)	< 0.0001
Progestin-only OCP use	101,612	150	14.76	5.45 (3.86, 7.70)	4.84 (3.41, 6.88)	< 0.0001
Intrauterine device (IUD)	882,454	462	5.24	1.96 (1.42, 2.70)	1.99 (1.44, 2.75)	< 0.0001
Levonorgestrel IUD	536,219	183	3.41	1.27 (0.90, 1.78)	1.25 (0.89, 1.76)	0.1974
Copper IUD	14,449	99	6.84	2.55 (1.77, 3.67)	2.59 (1.80, 3.74)	< 0.0001
Unknown IUD type	201,586	180	8.93	3.21 (2.28, 4.51)	3.59 (2.55, 5.05)	< 0.0001

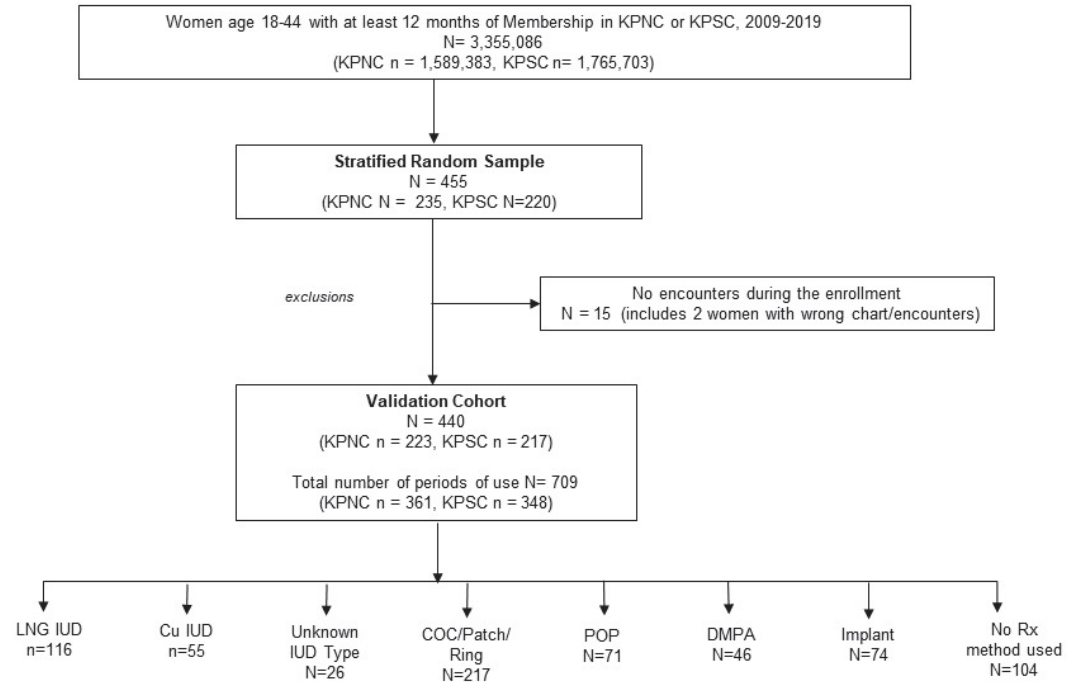
PID, pelvic inflammatory disease; STD, sexual transmitted disease limited to chlamydia and/or gonorrhea infection; DMPA, Depomedroxyprogesterone acetate; OCP, Oral contraceptive Pills.
[a]Incidence rate is shown per 10,000 Woman-years.
[b]Hazard ratios were adjusted for all factors listed in Table 10 and 11.

10.6 Aim 2c (Post-hoc analysis)

We selected a random sample of 455 women (KPNC, n=235 [220 + 15 algorithm testing cases]; KPSC, n=220), stratified by first contraceptive method (including no prescription method) used during the study time frame, as follows: 25% no method, 15% LNG-IUD, 10% Cu-IUD, 5% unknown IUD type, 15% COC, 5% patches or rings, 10% POP, 5% DMPA, 10% implants. Sample sizes for each contraceptive category were chosen to be large enough to provide acceptable precision of the positive predictive value (PPV) estimates based on 95% confidence intervals (CI). After excluding 15 women with no health care encounters during the enrollment period, incorrect charts or incorrect encounters, 440 women remained in the final validation cohort (Figure 7).

Of the 440 eligible women in the validation cohort, there were 336 women with 605 periods of method use (55 Cu-IUD, 116 LNG-IUD, 26 unknown IUD type, 160 COC, 71 POP, 57 patches or rings, 74 implants, and 46 DMPA) and 104 women who did not use a prescription method for a total of 709 periods of use (Figure 7) . The mean age of the cohort was 27.3 years (SD = 8.0).

10.6.1 Figure 7. Contraceptive Validation Population



Compared to the study population, the validation cohort was younger (65.2% < 30 years of age vs 57.5%) but had similar median census block family household income and race/ethnicity distributions (Table 12). Comparison of the KPNC and KPSC validation samples showed that the samples were similar in age distribution but KPNC had a larger proportion of non-Hispanic White and Asian/Pacific Islander women and a smaller proportion of Hispanic and non-Hispanic Black women. Median census block family household income was higher in the KPNC sample (Table 12).

Overall PPV of the electronic algorithm was 93.0% (95% CI 90.8-94.7). PPV by method was: copper IUD 100.0% (93.5-100.0), levonorgestrel IUD 96.6% (91.4-99.1), unknown IUD type 88.5% (69.9-97.6), COC 91.9% (86.5-95.6), POP 87.3% (77.3-94.0), patches or rings 91.2% (80.7-97.1), implant 83.8% (73.4-91.3), DMPA 97.8% (88.5-99.9). PPV for women with no prescription method use was 97.1% (91.8-99.4) (Table 13). Results by study site are presented in Appendix Tables 1 and 2. Of the 440 women in the validation cohort, 396 had all of their contraceptive method use periods confirmed as accurate, for a PPV of 90.0% (86.8-92.6).

Among the 104 women for whom no prescription contraceptive method use was identified by the algorithm, chart review revealed that 3 (0.03%) used a prescription method (1 each used COC, LNG-IUD and Cu-IUD) and 27 (26.0%) used a non-prescription method: 15 (14.4%) used condoms, 7 (6.7%) were sterilized, 2 (1.9%) used withdrawal or natural methods, and 3 (2.9%) used barrier methods, spermicides or other methods.

10.6.2 Table 12. Characteristics of the validation study sample compared to the study population

	Validation Sample			Study Population 2009-2019
	KPNC n=223	KPSC n=217	Total N=440	Total N = 3,355,086
Length of enrollment* in months, Mean (SD)	42.9 (34.6)	40.8 (32.7)	41.9 (33.7)	69.6 (62.1)
	N (%)	N (%)	N (%)	N (%)
Age at Cohort Entry, years				
<20	67 (30.0)	59 (27.2)	126 (28.6)	874,669 (26.1)
20-29	81 (36.3)	80 (36.9)	161 (36.6)	1,054,661 (31.4)
30-34	37 (16.6)	42 (19.4)	79 (18.0)	540,862 (16.1)
≥35	38 (17.0)	36 (16.6)	74 (16.8)	884,894 (26.4)
Race/ethnicity				
Non-Hispanic White	100 (44.8)	47 (21.7)	147 (33.4)	1,076,267 (32.1)
Non-Hispanic Black	13 (5.8)	23 (10.6)	36 (8.2%)	256,268 (7.6)
Hispanic	47 (21.1)	111 (51.2)	158 (35.9)	1,148,035 (34.2)
Asian/Pacific Islander	50 (22.4)	20 (9.2)	70 (15.9)	544,659 (16.2)
Other/Unknown	13 (5.8)	16 (7.4)	29 (6.6)	329,857 (9.8)
Family household income**				
< $30,000	5 (2.2)	12 (5.5)	17 (3.9)	99,241 (3.0)
$30,000-$49,999	27 (12.1)	69 (31.8)	96 (21.8)	615,871 (18.4)
$50,000-$69,999	36 (16.2)	50 (23.0)	86 (19.6)	793,292 (23.6)
$70,000-$89,999	56 (25.1)	41 (18.9)	97 (22.0)	713,280 (21.3)
≥ $90,000	99 (44.4)	44 (20.3)	143 (32.5)	1,127,317 (33.6)
Missing	-	1 (0.5)	1 (0.2)	6085 (0.2)
1st method used				
Copper IUD	24 (10.8)	22 (10.1)	46 (10.5)	57,973 (1.7)
Levonorgestrel IUD	32 (14.4)	33 (15.2)	65 (14.8)	162,281 (4.8)
IUD type unknown	13 (5.8)	10 (4.6)	23 (5.2)	35,099 (1.0)
Combined OCP	31 (13.9)	33 (15.2)	64 (14.5)	905,984 (27.0)
Progesterone-only OCP	23 (10.3)	21 (9.7)	44 (10.0)	97,665 (2.9)
Depot medroxyprogesterone acetate	13 (5.8)	11 (5.1)	24 (5.5)	108,240 (3.2)
Transdermal Patch/ Vaginal Ring	14 (6.3)	11 (5.1)	25 (5.7)	69,391 (2.1)
Implant	23 (10.3)	22 (10.1)	45 (10.2)	56,443 (1.7)
No prescription method used	50 (22.4)	54 (24.9)	104 (23.6)	1,862,010 (55.5)
Used >1 method	49 (22.0)	43 (19.8)	92 (20.9)	454,274 (13.5)

*If women had more than one enrollment period, only the first enrollment period was used
** Based on 2010 census block median income data

10.6.3 Table 13. Accuracy (PPV) of electronic algorithm compared to chart review by contraceptive method – Total (KPNC + KPSC)

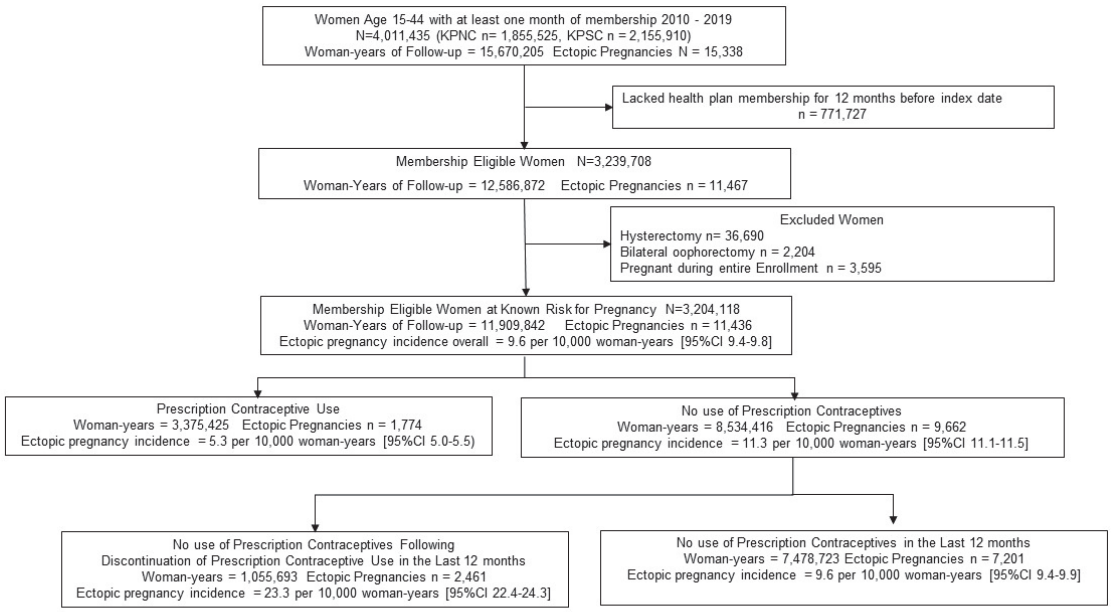
	Total N=709					
	Number of periods reviewed	Mean Number of days used [SD] Median (IQR)	Number use confirmed	Number uncertain	PPV (confirmed/ reviewed)	(95% CI)
Overall	709	466.1 (567.0) 227 (106-609)	659	11	93.0%	(90.8-94.7)
By Method						
Copper IUD	55	456.3 (407.9) 366 (125-758)	55	0	100.0%	(93.5-100.0)
Levonorgestrel IUD	116	572.9 (537.4) 389 (155-892)	112	0	96.6%	(91.4-99.1)
IUD type unknown	26	656.3 (621.9) 532 (214-884)	23	0	88.5%	(69.9-97.6)
Combined OCP	160	308.6 (436.4) 143 (106-355)	147	6	91.9%	(86.5-95.6)
Progesterone-only OCP	71	153.8 (101.4) 106 (106-187)	62	4	87.3%	(77.3-94.0)
Depot medroxyprogesterone acetate	46	153,3 (115.8) 100 (91-215)	45	0	97.8%	(88.5-99.9)
Transdermal Patch or Vaginal Ring	57	288.5 (379.3) 146 (106-359)	52	1	91.2%	(80.7-97.1)
Implant	74	489.9 (376.2) 417 (154-815)	62	0	83.8%	(73.4-91.3)
No prescription method used	104	979.1 (888.2) 731 (274-1446)	101	0	97.1%	(91.8-99.4)

California; PPV=positive predictive value; IUD=intrauterine device; OCP=oral contraceptive pills.

10.7 Aim 1c (Post-hoc analysis)

There were 4,011,435 women who were enrolled in a KPNC or KPSC health plan from 2010-2019; slightly over half were from KPSC (n= 2,155, 910, 53.7%) (Figure 8). 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 3,204,188 women with 11,909,842 woman-years of follow-up. Women who were excluded were more likely to be in the 20-29 age group than in population studied at index (40.8% in the excluded group vs. 33.1% in the study cohort, p<.0001) and more likely to have unknown/missing race-ethnicity (35.0% in the excluded group, 9.8% in the study cohort, p<.0001). They were also more likely to have median household income less than $50,000 (28.0% vs. 26.1%, p<.0001).

10.7.1 Figure 8. Ectopic Pregnancy Incidence in Women with Prescription Contraceptive Use and Non-use 2010 – 2019; Kaiser Permanente Northern and Southern California



The demographic characteristics of women in the study population by prescription contraceptive used are provided in Table 14. The mean time women were enrolled in the health plan was 3.7 $\pm$ 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.

10.7.2 Table 14. Demographics of the Study Population by Prescription Contraceptive Used During the Study Period

	Total	Only Used Combined Hormonal Contraceptives	Only Used Intrauterine Devices	Only Used DMPA	Only Used Progesterone-only Pill	Only Used Implant	Used More Than One Method	No Methods Used
	N = 3,204,118 (%)	n = 717,455 (22.4)	n = 236,669 (7.4)	n = 61,487 (1.9)	n = 45,620 (1.4)	n = 43,820 (1.4)	n = 379,494 (11.8)	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[1], 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

Data are column percents unless otherwise noted
[1] Family household median income obtained from 2010 census block data

The incidence of EP by contraceptive method is provided in Table 15. 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 2.1 (95% CI 1.5-2.9) and 2.1 (95% CI 1.5-2.8), respectively. EP incidence during prescription contraceptive use was highest for the POP at 17.2 (95% 15.0-19.8); however, this incidence was lower than the incidence during no use following discontinuation of a prescription method in the last 12 months (23.3 [95% CI 22.4-24.3]). EP incidence for the LNG-IUD (3.9 [95% CI 3.5-4.4]) was lower than the incidence for the Cu-IUD (8.0 [95% CI 6.9-9.2]); the confidence intervals did not overlap (Table 15).

10.7.3 Table 15. Incidence of Ectopic Pregnancies by Prescription Contraceptive Method 2010-2019

Method	Number of Ectopic Pregnancies	Woman-years	Incidence per 10,000 woman years	95% Confidence Interval
Combined Hormonal Contraceptive[1]	935	1,811,306	5.2	4.8-5.5
Levonorgestrel IUD	306	779,965	3.9	3.5-4.4
Copper IUD	195	243,918	8.0	6.9-9.2
IUD Type unknown	62	73,584	8.4	6.6-10.8
Depomedroxyprogesterone acetate	33	160,488	2.1	1.5-2.9
Progesting-only oral contraceptive	204	118,318	17.2	15.0-19.8
Implant	39	187,844	2.1	1.5-2.8
No use	7,201	7,478,724	9.6	9.4-9.9
No use following discontinuation of prescription contraceptive use in the last 12 months	2,461	1,055,693	23.3	22.4-24.3
Overall[2]	**11,436**	**11,909,842**	**9.5**	**9.3-9.7**

[1]Combined Hormonal contraceptives includes combined oral contraceptives, the transdermal patch, and the vagina ring; [2]Age-adjusted incidence based on the age distribution women age 15-44 in 2014

There were 2,274,062 women with 10,442,118 woman-years of observation time who enrolled in a health plan with an index date during 2010-2015 who were included in the sensitivity analysis (Table 16). 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 during no use following discontinuation of prescription contraceptives in the last 12 months (23.2 [95% CI 22.2-24.1]) and with POP use (17.2, 95% CI 14.9-19.9). Results by site are presented in the appendices. Since the results of the sensitivity analyses did not differ significantly from overall results, the sensitivity analyses were not done by site.

10.7.4 Table 16. Ectopic Pregnancy Incidence by Prescription Contraceptive Method 2010-2019; Kaiser Permanente Northern and Southern California - N=2,274,062. Sensitivity Analysis women with enrollment start 2010-2015

Method	Number of Ectopic Pregnancies	Woman-years	Incidence per 10,000 woman-years	95% Confidence Interval
Combined Hormonal Contraceptive	837	1,620,778	5.2	4.8-5.5
Levonorgestrel IUD	273	713,765	3.8	3.4-4.3
Copper IUD	182	223,621	8.1	7.0-9.4
IUD Type unknown	51	64,923	7.9	6.0-10.3
Depomedroxyprogesterone acetate	29	146,223	2.0	1.4-2.9
Progesting-only oral contraceptive	182	105,583	17.2	14.9-19.9
Implant	31	152,992	2.0	1.4-2.9
No use	6,259	6,468,957	9.7	9.4-9.9
No use following discontinuation of prescription contraceptive use in the last 12 months	2,189	945,278	23.2	22.2-24.1
Overall[1]	**10,033**	**10,442,118**	**9.4**	**9.2-9.6**

[1] Combined Hormonal contraceptives includes combined oral contraceptives, the transdermal patch, and the vagina ring; [2]Age-adjusted incidence based on the age distribution women age 15-44 in 2014

10.8 Aim 2d (Post-hoc analysis)

Among eligible women (N=3,204,098), we identified a total of 659,779 women that used a study contraceptive method (**Table 17**). Most of the study cohort (N=2,544,319, 79%) however, recently discontinued or were remote or non-users during the study period. Among these, 225,130 women discontinued contraceptive use recently (<1 year). Women who had a remote discontinuation or did not use a prescription contraceptive during the study period (N=2,319,189) were younger (mean age=27.4 [SD=9.5]) compared with women with current prescription contraceptive use (mean age=28.5 [SD=7.1]) or who had discontinued within the past year (mean age=28.5 [SD=7.2]) and less likely to be White (29% vs. 36-44% for others). There was no statistical difference on the household income between groups.

The overall incidence of EP was 9.5/10,000 person-years. The incidence rates among White, Black, Hispanic, Asian/Pacific Islander, and other/unknown racial/ethnic groups were 8.3, 15.0, 10.2, 9.4, and 3.8/10,000 person-years, respectively (**Table 18**). Hispanics (crude HR [cHR]: 1.23, 95% CI: 1.17-1.28), Blacks (cHR: 1.80, 95% CI: 1.70-1.92) and Asian/Pacific Islanders (cHR: 1.13, 95% CI: 1.07-1.20) were more likely to be diagnosed with EP compared to Whites. The association persisted for Hispanics and Blacks after adjustments for covariates listed in Tables 2 to 4. Compared with women aged 20-29 years, women aged 30-34 years were more likely to have EP diagnosis (incidence rates: 10.2 vs. 18.5/10,000 person-years, adjusted HR [aHR]: 1.40, 95% CI: 1.33-1.47). Multiparous women (aHR: 1.16, 95%CI: 1.11-1.22) and women who were former smokers (aHR: 1.19, 95% CI: 1.12-1.27) or current (aHR: 1.44, 95% CI: 1.36-1.52) were more likely to have EP diagnosis. There was a monotonic trend for decreasing incidence rate and EP risk with increasing household income. Household income of ≤$49,999 was significantly associated with EP diagnosis compared with an income of ≥$90,000. After adjusting for the same covariates used in building the propensity score model in the main analysis as the Cox regression models, the statistical significance persisted for adnexal surgery (aHR: 1.94, 95% CI: 1.76-2.14), but not for the remaining pelvic organ surgeries (**Table 19**). Tubal ligation/occlusion was inversely associated with reduced EP risk in both crude (cHR: 0.49, 95%CI: 0.40-0.59) and adjusted (aHR: 0.34, 95% CI: 0.28-0.41) models.

Compared to prescription contraceptive method discontinuation more than a year ago or non-use of prescription contraceptives during the study period, current use of all contraceptive methods except POP had a lower incidence of EP diagnosis (**Table 20**). When covariates were adjusted for, the risk of developing an EP was significantly lower among DMPA injection use (aHR: 0.16, 95% CI: 0.12-0.23), CHC (aHR: 0.49, 95%CI: 0.46-0.53), implant (aHR: 0.18, 95% CI: 0.13-0.25), levonorgestrel IUD (aHR: 0.30, 95%CI: 0.27-0.34), copper IUD (aHR: 0.64, 95% CI: 0.55-0.73) and IUDs of unknown type (aHR: 0.73, 95% CI: 0.57-0.94) compared to remote or non-use during the study period. Conversely, periods of non-prescription contraceptive use in which a method was recently discontinued within the past year had a higher EP incidence rate (23.3 vs. 9.5/10,000 person-years; aHR: 1.76, 95% CI: 1.68-1.84).

A post hoc sensitivity analysis that included spontaneous abortion and stillbirth as censoring events did not affect our results (data not shown).

10.8.1 Table 17. Distribution of cohort characteristics based on earliest contraceptive method use status during the study period

Characteristics	Total N=3,204,098	Any Contraceptive[a] N=659,779	Non-Use	
			Discontinued ≤ 1 year[b] N= 225,130	Discontinued > 1 year[c] N=2,319,189
Age, Mean (SD)	27.7 (8.9)	28.5 (7.1)	28.5 (7.2)	27.4 (9.5)
Age, year, n (%)				
15-19	814,120 (25.4)	75,351 (11.4)	26,770 (11.9)	711,999 (30.7)
20-29	1,013,219 (31.6)	307,457 (46.6)	101,111 (44.9)	604,651 (26.1)
30-34	527,473 (16.5)	134,678 (20.4)	48,080 (21.4)	344,715 (14.9)
35-44	849,286 (26.5)	142,293 (21.6)	49,169 (21.8)	657,824 (28.4)
Race/Ethnicity, n (%)				
Non-Hispanic White	1,031,252 (32.2)	286,821 (43.5)	81,613 (36.3)	662,818 (28.6)
Non-Hispanic Black	243,843 (7.6)	44,130 (6.7)	20,618 (9.2)	179,095 (7.7)
Hispanic	1,103,370 (34.4)	199,693 (30.3)	79,247 (35.2)	824,430 (35.5)
Asian/Pacific Islander	528,238 (16.5)	89,629 (13.6)	30,514 (13.6)	408,095 (17.6)
Other/Unknown	297,395 (9.3)	39,506 (6.0)	13,138 (5.8)	244,751 (10.6)
Smoking Status, n (%)				
Never	2,254,651 (70.4)	506,901 (76.8)	167,075 (74.2)	1,580,675 (68.2)
Former	199,053 (6.2)	54,649 (8.3)	19,682 (8.7)	124,722 (5.4)
Current	260,860 (8.1)	63,931 (9.7)	25,193 (11.2)	171,736 (7.4)
Unknown	489,534 (15.3)	34,298 (5.2)	13,180 (5.9)	442,056 (19.1)
Parity, n (%)				
Nullipara	558,789 (17.4)	207,077 (31.4)	68,636 (30.5)	283,076 (12.2)
Multipara	860,369 (26.9)	229,671 (34.8)	86,576 (38.5)	544,122 (23.5)
Unknown	1,784,940 (55.7)	223,031 (33.8)	69,918 (31.1)	1,491,991 (64.3)
Household income[d], USD, n (%)				
< 30,000	138,423 (4.3)	24,502 (3.7)	9,958 (4.4)	103,963 (4.5)
30,000-49,999	698,270 (21.8)	129,772 (19.7)	49,508 (22.0)	518,990 (22.4)
50,000-69,999	856,655 (26.7)	175,497 (26.6)	60,910 (27.1)	620,248 (26.7)
70,000-89,999	691,830 (21.6)	149,020 (22.6)	48,868 (21.7)	493,942 (21.3)
≥ 90,000	812,068 (25.3)	179,763 (27.2)	55,445 (24.6)	576,860 (24.9)
Unknown	6,852 (0.2)	1,225 (0.2)	441 (0.2)	5,186 (0.2)

Abbreviations: SD; Standard Deviation; USD, United States Dollar. [a]Combined Oral Contraceptive/Patch/Ring, Progestin-only Oral Contraceptive Pills, Implants, Depomedroxyprogesterone acetate, Intrauterine Device; [b]Patient stopped using contraceptive within 1 year prior to first method start; [c]Patient stopped using contraceptive >1 year prior to first method start; [d]Median family household income based on census tract of residence; All differences in proportion are statistically significant ($P < .001$)

10.8.2 Table 18. Incidence rates and hazard ratios expressing the association of demographic characteristics with ectopic pregnancy risk

Characteristics	Person-Year N=11,904,529	EP N=11,304	Rate[a] 9.50	Hazard Ratio (95% CI) Crude	Hazard Ratio (95% CI) Adjusted[b]
Age, year					
15-19	2,005,309	306	1.53	0.14 (0.13, 0.16)	0.18 (0.16, 0.20)
20-29	3,713,131	3,793	10.22	1.00 (reference)	1.00 (reference)
30-34	1,999,229	3,696	18.49	1.80 (1.72, 1.88)	1.40 (1.33, 1.47)
35-44	4,186,860	3,509	8.38	0.83 (0.79, 0.87)	0.62 (0.59, 0.66)
Race/Ethnicity					
Non-Hispanic White	3,931,541	3,269	8.31	1.00 (reference)	1.00 (reference)
Non-Hispanic Black	993,777	1,489	14.98	1.80 (1.70, 1.92)	1.65 (1.55, 1.76)
Hispanic	4,286,624	4,375	10.21	1.23 (1.17, 1.28)	1.24 (1.18, 1.30)
Asian/Pacific Islander	2,039,629	1,924	9.43	1.13 (1.07, 1.20)	1.03 (0.97, 1.09)
Other/Unknown	652,959	247	3.78	0.45 (0.40, 0.52)	0.56 (0.49, 0.64)
Household income[c], USD					
< 30,000	498,802	579	11.61	1.38 (1.26, 1.51)	1.15 (1.05, 1.26)
30,000-49,999	2,533,126	2,651	10.47	1.24 (1.18, 1.31)	1.09 (1.03, 1.15)
50,000-69,999	3,207,015	3,070	9.57	1.14 (1.08, 1.20)	1.04 (0.99, 1.10)
70,000-89,999	2,608,426	2,429	9.31	1.10 (1.04, 1.17)	1.05 (0.99, 1.11)
≥ 90,000	3,042,375	2,563	8.42	1.00 (reference)	1.00 (reference)
Unknown	14,784	12	8.12	0.97 (0.55, 1.70)	1.19 (0.67, 2.10)
Parity					
Nullipara	2,838,671	3,328	11.72	1.00 (reference)	1.00 (reference)
Multipara	4,706,044	5,869	12.47	1.07 (1.03, 1.12)	1.16 (1.11, 1.22)
Unknown	4,359,814	2,107	4.83	0.39 (0.37, 0.41)	0.68 (0.65, 0.73)
Smoking Status					
Never	8,616,280	8,076	9.37	1.00 (reference)	1.00 (reference)
Former	871,865	1,143	13.11	1.40 (1.31, 1.49)	1.19 (1.12, 1.27)
Current	976,386	1,422	14.56	1.55 (1.47, 1.64)	1.44 (1.36, 1.52)
Unknown	1,439,997	663	4.60	0.49 (0.45, 0.53)	0.65 (0.60, 0.71)

Abbreviations: CI, confidence interval; EP, ectopic pregnancy; USD, United States Dollar
[a]Incidence rate is shown per 10,000 person-years; [b]Hazard ratios were adjusted for covariates listed in Tables 2 and 3; [c]Median family household income based on census tract of residence

10.8.3 Table 19. Incidence rates and hazard ratios expressing the association of potential medical- and obstetrical-related risk factors with ectopic pregnancy risk

History of potential risk factors	Total Person-Year	EP (N)	Incidence Rate[a]	Hazard Ratio (95% CIs)	
				Crude	Adjusted[b]
Ectopic Pregnancy					
No	11,901,273	11,270	9.47	1.00 (reference)	1.00 (reference)
Yes	3,256	34	104.44	10.9 (7.77, 15.26)	3.01 (2.14, 4.25)
Sexually Transmitted Disease					
No	11,477,498	10,425	9.08	1.00 (reference)	1.00 (reference)
Yes	427,031	897	20.58	2.28 (2.13, 2.45)	1.80 (1.68, 1.94)
Pelvic Inflammatory Disease					
No	11,875,477	11,199	9.43	1.00 (reference)	1.00 (reference)
Yes	29,052	105	36.14	3.82 (3.15, 4.63)	1.44 (1.18, 1.75)
Infertility					
No	11,489,874	9,233	8.04	1.00 (reference)	1.00 (reference)
Yes	414,655	2,071	49.95	6.46 (6.15, 6.78)	4.57 (4.34, 4.81)
Endometriosis					
No	11,467,103	10,469	9.13	1.00 (reference)	1.00 (reference)
Yes	437,426	835	19.09	2.10 (1.96, 2.26)	1.24 (1.15, 1.33)
Congenital Malformation					
No	11,870,701	11,192	9.43	1.00 (reference)	1.00 (reference)
Yes	33,828	112	33.11	3.50 (2.91, 4.22)	1.46 (1.21, 1.76)
Pelvic Organ Surgeries					
Cesarean Section					
No	10,740,030	9,823	9.15	1.00 (reference)	1.00 (reference)
Yes	1,164,499	1,481	12.72	1.39 (1.32, 1.47)	0.96 (0.91, 1.02)
Tubal ligation/occlusion					
No	11,676,346	11,196	9.59	1.00 (reference)	1.00 (reference)
Yes	228,183	108	4.73	0.49 (0.40, 0.59)	0.34 (0.28, 0.41)
Myomectomy					
No	11,856,098	11,185	9.43	1.00 (reference)	1.00 (reference)
Yes	48,431	119	24.57	2.59 (2.16, 3.11)	0.87 (0.72, 1.05)
Adnexal surgery					
No	11,766,203	10,782	9.16	1.00 (reference)	1.00 (reference)
Yes	138,326	522	37.74	4.14 (3.79, 4.53)	1.94 (1.76, 2.14)
Appendectomy					
No	11,799,392	11,194	9.49	1.00 (reference)	1.00 (reference)
Yes	105,137	110	10.46	1.10 (0.91, 1.33)	1.01 (0.83, 1.21)
Any pelvic surgery					
No	10,426,117	9,192	8.82	1.00 (reference)	1.00 (reference)
Yes	1,478,412	2,112	14.29	1.63 (1.56, 1.72)	1.03 (0.98, 1.08)

Abbreviations: EP, ectopic pregnancy; CI, confidence interval. [a]Incidence rate is shown per 10,000 person-years; [b]Hazard ratios were adjusted for factors listed in Tables 2 and 3; [c]Patient stopped using contraceptive >1 year prior to each method start; [d]Patient stopped using contraceptive within 1 year prior to each method start

10.8.4 Table 20. Incidence rates and hazard ratios expressing the association between contraceptive methods and ectopic pregnancy risk.

Contraceptive Method	Total Person-Year	EP (N)	Incidence Rate[a]	Hazard Ratio (95% Confidence Intervals)	
				Crude	Adjusted[b]
Non-Use (discontinued > 1 year)[c]	7,474,329	7,079	9.47	1.00 (reference)	1.00 (reference)
Non-Use (discontinued ≤ 1 year)[d]	1,055,137	2,458	23.30	2.47 (2.36, 2.59)	1.76 (1.68, 1.84)
DMPA	160,474	33	2.06	0.22 (0.15, 0.31)	0.16 (0.12, 0.23)
CHC use	1,811,214	934	5.16	0.55 (0.51, 0.58)	0.49 (0.46, 0.53)
Progestin-only OCP use	118,305	204	17.24	1.82 (1.59, 2.10)	1.13 (0.99, 1.31)
Implant	187,822	39	2.08	0.22 (0.16, 0.30)	0.18 (0.13, 0.25)
Intrauterine Device (IUD)	1,097,247	557	5.08	0.53 (0.49, 0.58)	0.40 (0.37, 0.44)
Levonorgestrel IUD	779,809	303	3.89	0.41 (0.36, 0.46)	0.30 (0.27, 0.34)
Copper-containing IUD	243,849	192	7.87	0.83 (0.72, 0.95)	0.64 (0.55, 0.73)
Unknown IUD type	73,589	62	8.43	0.90 (0.70, 1.15)	0.73 (0.57, 0.94)

Abbreviations: EP, ectopic pregnancy; DMPA, Depomedroxyprogesterone acetate; CHC, Combined Hormonal Contraceptives (including oral contraceptive, transdermal patch and vaginal ring) OCP, Oral Contraceptive Pills; [a]Incidence rate is shown per 10,000 person-years; [b]Hazard ratios were adjusted for factors listed in Tables 2 and 3; [c]Patient stopped using contraceptive >1 year prior to each method start; [d]Patient stopped using contraceptive within 1 year prior to each method start

11. Discussion

11.1.1 Validation Study

We found that our enhanced version of an algorithm that was previously validated by Scholes et al. in 2011 for identification of ectopic pregnancies using electronic data had good sensitivity (97.6%) and negative predictive value (94.6%) and performed slightly better than the original algorithm. Use of administrative and claims records along with electronic health records provides a unique opportunity to conduct pharmacoepidemiologic studies as well as to investigate the trends of selected disorders such as ectopic pregnancy. For conditions such as ectopic pregnancy, which may be evaluated over the course of one or more clinical encounters with a diagnosis confirmed or ruled out, it can be difficult to identify true cases using electronic chart abstraction. Scholes et al. developed the original algorithm using a classification and regression tree (CART) analysis. We made minor modifications to the algorithm to incorporate equivalent ICD-10 diagnostic and procedure codes and to take into account other coding differences unique to the current electronic health record (i.e. new medication codes) and clinical practice (i.e. increasing use of telephone encounters).

We validated both algorithms (the original and enhanced version) and demonstrated that addition of ICD-10 codes did not decrease the accuracy of the algorithm. The accuracy of electronic data abstraction to identify surgical management of ectopic pregnancy was good with overall accuracy of 92%. Our results are limited in that they may not be generalizable to health systems with different clinical practice patterns (i.e. non-closed health care system). There is a potential for missed cases due to miscoding, as well as receipt of care outside of the system that was not captured in the claims databases; however, this is probably small. Overall, the validation study allows us to be confident of the results of our primary study to assess ectopic pregnancy incidence and trend overtime and incidence among populations of interest such as contraceptive users.

11.1.2 Aim 1a/2b

Ectopic pregnancy occurred in about 1.5% of pregnancies in this population-based study and increased over the period from 2009 to 2018. Our data demonstrates that ectopic pregnancy continues to be a persistent source of reproductive health morbidity. Ectopic pregnancy is potentially life threatening and has important health consequences. Half of women with ectopic pregnancies in our population were treated surgically exposing them to potential treatment related complications. While mortality has declined significantly in the last 2 decades and is estimated to be less than 0.5 deaths per 100,000 live births, affected women also suffer significant morbidity including greater risk of another ectopic pregnancy and future infertility.[1,16]

The annual age-adjusted incidence of ectopic pregnancy of 14.5 per 1,000 pregnancies in 2010 in our study is fairly consistent with the rate of 15.0 per 1,000 pregnancies reported by Trabert et al. in 2005-2007 in a population-based study conducted in Group Health Cooperative, a nonprofit, mixed model healthcare system in Washington State and western Idaho.[6,7] In the study by Trabert et al., the ectopic pregnancy incidence of 18.2 per 1,000 pregnancies estimated in 1993-1995 was similar to the national incidence rate of 19.7 per 1,000 pregnancies estimated by the CDC in 1992.[4] Trabert et al documented a slight decline in the rate in their population over the ensuing 12 years. It is not known if our data reflect a new national trend of increasing ectopic pregnancy incidence. In the CDC study, the ectopic pregnancy rate was estimated using combined data from the National Hospital Discharge Survey and the National Ambulatory Medical Care Survey. In 2002, the CDC reported that reliable estimates of the ectopic pregnancy rate could no longer be estimated by

combining available nationally representative data sets due to the high likelihood of multiple counting of cases.[17] The consistency of the findings across populations and time frames using comprehensive electronic health data from Kaiser Permanente and Group Health Cooperative (now Kaiser Permanente Washington) support the validity of using health system data for surveillance of important reproductive health conditions.[5,7]

The proportion of ectopic pregnancy cases managed surgically (52%) is higher than expected given the decreasing trend seen in the study by Trabert et al. and only a third of cases managed surgically in 2005-2007.[6,7] It is possible that there are different practice patterns in our health systems compared to Group Health Cooperative in Washington. Alternatively, it is possible that with increasing utilization of minimally invasive surgery, the benefit associated with prompt definitive diagnosis and treatment with surgical management may outweigh surgical risks and is preferred equally to medical treatment. In a study by Hsu et. al. which examined ectopic pregnancy management from 2006-2015 using data from the Perspective all-payer hospital database, 78% of ectopic pregnancy cases were treated surgically.[18] These higher rates however are most likely related to the in-patient data source used in the study.

The incidence of ectopic pregnancy appeared stable over the study period when estimated as a proportion of women of reproductive age in the population; however, it appeared to increase when estimated as a proportion of pregnancies. Estimating ectopic pregnancy incidence rates using the overall population of women of reproductive age as the denominator is important but can mask important trends. In our population the ectopic pregnancy rate per 1,000 pregnancies increased due to decreasing pregnancy rate and relatively constant ectopic pregnancy rate over the study period. Estimating ectopic pregnancy incidence as a proportion of pregnancies also provides insight into underlying epidemiology which can be helpful for clinical vigilance. The disparity by age, with women age 40-44 years having the highest incidence per 1,000 pregnancies, was highlighted because the number of ectopic pregnancies is disproportionately higher for older women who have relatively fewer pregnancies compared to younger women. Age disparities have also been observed in national surveillance studies and Medicaid populations.[19,20]

Our study has several strengths including large number of ectopic pregnancies and a diverse community-based population that is broadly representative of women in California. Use of a validated algorithm for case ascertainment allowed us to utilize automated case-finding with good capture of the outcome of interest. Several limitations should also be considered. Our estimates of ectopic pregnancy incidence rates may overestimate the true rate due to under counting of induced abortions that occurred outside of the system and because women seeking abortions may be at a lower risk for ectopic pregnancy than women with desired pregnancies.[21,22] Spontaneous abortions were not included because reporting of these events is incomplete and to maintain consistency with other surveillance studies which did not include spontaneous abortions in the denominator. We also did not include the relatively small number of stillbirths in the denominator. Our healthcare system data may not be nationally representative or generalizable to other health systems (i.e. fee-for service and safety net systems); however, it serves as the most complete source of data on women at-risk for ectopic pregnancy. Use of comprehensive health system data has supplanted national surveillance data because it is difficult to extract incidence data from disparate inpatient and outpatient sources.

11.1.3 Aim 1b

Two- thirds of ectopic pregnancies in our population occurred in women who used OCPs, an IUD or DMPA during the study period; however only a small proportion of those ectopic pregnancies occurred with current or recent contraceptive use. It appears that ectopic pregnancy incidence was

lower for women with current or recent contraceptive use compared to the population overall; however, the rates are not directly comparable because exclusion criteria were applied in the contraceptive analysis that were not applied in the overall analysis. To improve capture of contraceptive use periods, we required a lookback period to identify contraceptive use that started before the study period such as an IUD insertion, which reduced the size of the cohort for the contraceptive analysis. We did not require a lookback period for the cross- sectional analysis to calculate the overall ectopic pregnancy incidence, making the incidence rates not directly comparable.

Among women with current contraceptive use, ectopic pregnancy incidence appeared highest in women with current POP use and it appeared lowest for women with DMPA use. Incidence appeared intermediate for women with IUD and COC use. Our data appear to indicate that POPs use may pose a higher risk of ectopic pregnancy than other methods. There is a consensus that available effective contraceptive methods reduce the absolute risk of ectopic pregnancy by lowering the risk of pregnancy overall. However, when there is method failure, women using intrauterine devices, and some progestin-only contraceptives have been shown to be at higher risk for ectopic pregnancy than women in the general population and women using combined oral contraceptives or barrier methods.[11-13] Our results seem consistent with these studies. The ectopic pregnancy incidence for known copper IUD users in our study was similar to rates in the EURAS prospective clinical trials.[23] Ectopic pregnancy incidence was 6.8 per 10,000 woman-years for copper IUD users in our study compared to 8.0 per 10,000 woman-years in the EURAS trial. Our rate of 3.4 ectopic pregnancies per 10,000 woman-years for levonorgestrel IUD users was higher compared to 2.0 per 10,000 woman-years in the EURAS trial. The only other published cohort study of ectopic pregnancy incidence was a population study of women of reproductive age living in Beijing by Zhang et al. They found an incidence of ectopic pregnancy of 5.4 per 10,000 married women using contraceptives, which is similar to our overall crude rate of 5.3 per 10,000 woman-years for all methods. Their rates for married IUD users and OCP users were 6.5 and 2.1 per 10,000 woman-years respectively. They did not examine ectopic pregnancy incidence by OCP type or IUD type.

The retrospective nature of our study and need to have a look back period to capture ongoing contraceptive use may have led to bias and under capture of some method users. The woman-years of POP use was relatively small leading to variation in the rate from year to year. Inability to identify IUD type for women who entered the system with an IUD limits our interpretation on incidence of ectopic pregnancy by IUD type. Approximately a quarter of IUD observation time was attributed to women with unknown IUD type. We also lack ability to determine method start and stop dates in women who either enter or leave the system with an existing IUD. Misclassification in our algorithm as a result of assumptions made about when to impute stop dates for women entering the system with an IUD or with unknown IUD type could lead to inaccurate stop dates for women with unknown IUD types and could affect the number of ectopic pregnancies estimated for this group. Additional validation of our contraceptive algorithms would be helpful to improve the algorithms to have better capture of method use.

11.1.4 Aim 2a

Our large socio-demographically diverse population-based cohort study of women with contraceptive use corroborates findings from earlier studies on potential risk factors for ectopic pregnancy. When considering age as a risk factor, women who are at the ends of the childbearing spectrum are at lower risk for ectopic pregnancy because they have fewer pregnancies. However as

demonstrated in Aim 1a, older women with pregnancies are at higher risk of ectopic pregnancy. Our study is consistent with findings of previous studies demonstrating non-Hispanic black or Hispanic race-ethnicity, low socioeconomic status, history of infectious diseases, and smoking are associated with ectopic pregnancy. The two risk factors which appeared to confer the largest magnitude of risk for ectopic pregnancy were previous history of ectopic pregnancy and history of infertility. In this retrospective cohort study, ascertainment of ectopic pregnancy history was based on history or incident case during the study period. We also used several indicators of history of infertility including diagnostic codes and evidence of fertility treatments. Our study population included only women who were using oral contraceptives, IUDs, and DMPA which allowed us to examine the odds of ectopic pregnancy associated with different contraceptive methods. It also minimizes the risk of bias due to factors related to contraceptive use that are difficult to measure retrospectively including sexual activity, pregnancy intentions, and life style factors.

The vast majority of studies of ectopic pregnancy risk factors have been case-control studies using pregnant women as controls. The fundamental problem in the interpretation of case control studies is control definition. If a risk factor reduces fertility, the association with ectopic pregnancy is dependent on the selection of the control group. Case-control studies with pregnant controls demonstrate a higher association with factors that decrease fertility (i.e. chlamydia infection).[10,24] Currently, there is conflicting evidence on the effect of tobacco smoking on ectopic pregnancy risk, some reported no association and others reported significantly increased risk.[25-27] This conflicting data is most likely due to differences in controls.[28] The benefit of our cohort study is avoidance of such selection bias. In the current study, we demonstrated that current smoking was an independent risk factor for ectopic pregnancy, while former smoking was not significantly associated with risk of ectopic pregnancy. While elevated risk associated with smoking may be due to physiologic effects on the fallopian tube; however, risk associated with race/ethnicity and socioeconomic status are more likely due to residual confounding.[27]

Studies have also shown conflicting results related to pelvic surgery. Pelvic surgery can cause tubal factor infertility and thus case-control studies with pregnant controls will magnify the risk while non-pregnant controls may mask risk. After adjusting for multiple risk factors, myomectomy was the only type of pelvic surgery in which an elevated risk was demonstrated. This is consistent with retrospective cohort studies of women who have undergone myomectomy and attempted to conceive afterwards and women undergoing assisted reproductive technologies; however it has not been demonstrated in unselected populations before.[29,30] Previous studies have shown associations between a history of cesarean section and adnexal surgery with subsequent increased risk of ectopic pregnancy.[31] Although we observed significant differences in the incidences and increased risk in ectopic pregnancy in women with a history of cesarean delivery and adnexal surgery in crude analyses, no significant associations were observed after adjustment for baseline characteristics, potential risk factors, and contraceptive methods.

We demonstrated that among this cohort of women using contraceptives, women with POP use had the highest incidence of ectopic pregnancy and their risk was increased (5-fold) compared to women with DMPA use. Ectopic pregnancy risk was also elevated for women with COC (2-fold) and known copper IUD (2-fold) compared to DMPA use. Previous studies have shown elevated risk with IUDs with higher risk for copper compared to women with levonorgestrel IUD use.[23] Our analysis of risk associated with contraceptive use is preliminary pending further validation of contraceptive method ascertainment. The elevated incidence of ectopic pregnancy among women with unknown IUD type is probably related to misclassification and our algorithm which may have inaccurately imputed some stop dates which could falsely increase the number of ectopic

pregnancies seen with IUDs of unknown type. We plan to conduct additional analyses to test the effects of changes in the algorithm on ectopic pregnancy rates.

Strengths of this study include its population-based nature and access to data on multiple potential risk factors. Furthermore, data extracted from the Kaiser Permanente's integrated electronic health records has been validated for demographic and pregnancy related epidemiological studies. Our study has limitations worth noting. Some data on smoking was missing and we did not include information on Body Mass Index limiting our ability to examine the extent to which these risk factors are associated with ectopic pregnancy. The retrospective nature of the study may result in residual confounding for some variable due to unmeasured bias. The vast majority of studies of ectopic pregnancy were done in the 80's and 90's, prior to changes in the epidemiology of childbearing age, use of assisted reproductive technologies, and a broader array of contraceptive methods. The ability to abstract information on contraceptive use from electronic medical records provides the unique opportunity to assess complications of method failure in an efficient manner.

11.1.5 Aim 2c (Post-hoc analysis)

The electronic algorithm identified contraceptive use periods with high accuracy. The overall PPV was 93.0%. The algorithm was particularly accurate for methods requiring procedures for initiation or discontinuation; the PPV was above 90% for LNG- and Cu-IUDs, DMPA, COC, and patches and rings. IUDs of unknown type, POP and implants had very good PPVs ranging between 83.8% and 88.5%. This indicates that when prescription contraceptive use is identified using this algorithm it is highly likely that method use can be inferred and used for analysis of outcomes associated with use.

Pharmacologic databases in Scandinavia and the United States4 have been used to evaluate associations between contraceptive exposure and disease outcomes, including thromboembolism, breast cancer, ectopic pregnancy, stroke and myocardial infarction.[32-35] Typically, those studies did not employ natural language processing of clinical notes to enhance the capture of accurate contraceptive use, such as IUD removals, as we did, and thus rely on more assumptions in the absence of contraceptive device insertion and removal codes.

While there are many studies that used pharmacy records for identification of contraceptive use, we were unable to identify any published validation studies of their methods. One reason is that it is very difficult to assess exact periods of use for prescription methods that are dispensed from pharmacies using EHR data; we looked for any evidence to confirm use of the method but it is not possible to know for certain if a women used a method for the entirety of the observation time we assigned. It is not feasible or practical to contact women and interview them to see if they used methods. However, EHRs serve a useful purpose when prospective or direct patient contact cannot be feasibly done.

The strengths of this study include the use of natural language processing to improve the accuracy of our algorithm and the large, diverse cohort of women in each contraceptive use category. The long enrollment in the health plans for many of the women in the cohort provided the ability to validate periods of method use despite complex use patterns. A limitation of the study is the lack of reliable or consistent data for care received prior to joining KP or obtained outside of KP during membership; we assumed that women who had contraceptive device removal codes or contraceptive surveillance codes and no insertion codes entered the health plan with that device already in place this may have led to overestimation of observation time for IUDs and Implants. These results suggests the contraceptive algorithms will be useful for future studies of outcomes associated with contraceptive use.

11.1.6 Aim 1c (Post-hoc analysis)

Our study 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 during POP use. The highest EP incidence, however, was observed during non-use following discontinuation of a prescription contraceptive in the last 12 months. This is one of the only and largest studies to document the comparative and protective effect of contraceptives on EP. During periods of non-use, we did not have information about sexual activity or use of over-the-counter contraceptive methods. We hypothesize that periods of non-use following method discontinuation serve as a proxy for periods when women who are sexually active may be abstaining, or are sexually active and using over-the-counter methods, no methods, or trying to conceive.

The only other population-based study that we are aware of that assessed EP incidence for contraceptive users and non-users was the study by Zhang et al. which also demonstrated that current contraceptive users have a lower incidence of EP than non-contraceptive users.[14] 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 1,000 compared to 0.54 per 1,000 married women using contraceptives.[14] 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 provides more granularity by IUD and oral contraceptive pill type.

Other non-comparative studies of specific methods from clinical trial data have found that the incidence of EP is higher for the POP, and have suggested the incidence may be higher than that of women not using contraceptives.[36] While our data also demonstrates higher incidence of EP with the POP, the comparative analysis does not confirm that the incidence of EP with POP use is greater with non-use of contraception. Schultheis et al. did a comparative analysis of EP incidence with use of contraceptive methods in the CHOICE study, a prospective cohort of women who were provided no-cost contraception and followed for three years.[37] They 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 study has several strengths in addition to a large number of EPs. We used validate algorithms that were developed/adapted for this study. We had 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 of Northern California except for individuals at the lower and upper extremes of income.[38]

Our study also has limitations. The study may not be generalizable to non-insured populations in other health care systems. We used pharmacy records to determine the exposure to oral contraceptives, transdermal patches, and vaginal rings which provides information on methods dispensed not actual use. The contraceptive validation demonstrated 93%-100%; however, accuracy for prescribed methods was lower than methods which required procedures for initiation and discontinuation. We were unable to identify IUD type for some IUD insertions that occurred before enrollment in the Kaiser Permanente healthcare 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 women becoming pregnant on various methods. Estimating the number of pregnancies that occurred during

contraceptive use is beyond the scope of this analysis as contraceptive method failures are not necessarily coded as such in the EHR. Information on sexual activity or use of non-prescription 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.

11.1.7 Aim 2d (Post-hoc analysis)

This study provided important data on the protective effect of contraceptive use on the incidence of EP diagnosis. After controlling for well documented risk factors in literature, our large population-based cohort study revealed that except for POP, current use of prescription contraceptive was associated with a reduced EP risk compared to non-use of contraceptive. EP risk was increased in recent discontinuation of prescription contraceptive (within 1 year of a method start) compared to remote or no use during the study period. This is most likely explained by the fact that >80% of women stop contraception because they desire a pregnancy, and get pregnant within 1 year after stopping contraception.[39] Therefore, it is the most likely period for EPs to occur. Our EP risk estimate probably underestimated the actual risk without contraceptive use as the reference method, remote or no contraceptive use during the study period included observation time of women who never used contraception, part of which represents time when women were not sexually active, used non-prescription methods, or were not at-risk of pregnancy for other reasons such as same sex partners. We observed a 66% reduction in EP risk among women who underwent a tubal ligation/occlusion due to it being among the most effective form of contraceptive methods.

Results
The findings from this sociodemographically diverse population-based study corroborated findings from earlier studies on reproductive risk factors for EP, including multiparity, smoking, and history of medical, obstetrical, as well as gynecological risk factors.[26,31,40-44] Race/ethnicity and income were independent risk factors for EP diagnosis; it was increased for Black women and women with lower income.

The two risk factors which appeared to confer the largest magnitude of EP risk were previous history of EP and history of infertility. Increased risk of recurrence in individuals with a prior history of EP include sequelae of PID and a history of surgery on the fallopian tubes or within the pelvis, both of which were also risk factors identified in our data. If not recognized early and managed promptly, symptomatic/asymptomatic PID can lead to permanent changes on affected fallopian tubes, diminishing its patency, which can be a source of recurrent EP.[45,46] A history of conservative surgical management of a prior EP has also been implicated as a contributing factor for a subsequent EP.[47] ART is a widely used infertility treatment and its use has increased recently. Factors which lead to infertility, such as tubal disease may contribute to increased EP risk; however, other unknown factors that lead to infertility may also contribute. Infertility treatment-related ovarian hyperstimulation has been suggested to induce pro-inflammatory cytokines/chemokines release that may potentially disrupt optimal interactions among the embryo, fallopian tube, and endometrium.[48] Furthermore, fertility treatments such as *in-vitro* fertilization may overexpress adhesion molecules in the fallopian tubes and cause ciliary dysfunction leading to EPs.[49]

There is conflicting evidence in the literature on the effect of cigarette smoking on EP risk, some have reported no association[50,51] and others an increased risk.[42,43,52] The results of the current study, however, suggested that not only current smoking but also former smoking increases risk. Therefore, our findings suggest cigarette smoking, even when discontinued before pregnancy, can have long-

term effect on EP risk and never having a history of smoking is protective against EP. Although, the pathophysiology of its effect is largely unknown, it has been suggested that cotinine, a nicotine metabolite, impairs tubal motility by altering tubal Prokineticin Receptor 1 expression and changes in the microenvironment.[53]

Clinical Implications

Studies have demonstrated associations between a history of cesarean birth with subsequent EP risk.[26,31,44] Although our finding from unadjusted analyses concurred with previous findings, the observed association was rendered non-significant after adjustment for potential confounders suggesting that it was not an independent risk factor.

The most likely mechanism that contraceptives are protective of EP is by preventing ovulation or fertilization and therefore pregnancy. POPs do not consistently inhibit ovulation and are less effective than combined hormonal contraception, which may explain why there did not appear to be a protective effect compared to no current use or remote use. Compared to women who were not using any prescription contraceptive method or those that discontinued their use for more than a year, EP risk was lower for women who were using DMPA (84%) and implant (82%) methods. Bouyer et al., showed a higher EP risk in women using IUDs,[54] a finding that was not supported by our analysis. Of long-acting reversible contraceptives users, women who had been using levonorgestrel or copper IUD had 70% and 36%, respectively, lower EP risk. The benefit of contraceptives in reducing EP risk may largely be because they prevent pregnancy.[55,56]

After controlling for known risk factors for EP, contraceptive use remained a protective factor. This information is important for counseling patients about the benefits of contraception, especially women who may be at risk for EP. Women with a prior history of EP and those with a history of infertility should be counseled to use effective contraceptive if they are at risk and not trying to conceive. Women with a history of infertility may not be motivated to use contraception; however, our data suggest benefit. While POPs did not appear protective of EP, the absolute risk was low and was not increased compared to no contraceptive use (with recent discontinuation). Therefore, for most women the contraceptive benefit of POPs may outweigh EP risk.

Research Implications

We demonstrated the important role of how a prior history of EP and infertility contribute to EP risk. However, the etiological mechanisms have not been fully elucidated and represent an area for further investigation. Moreover, this study highlights a disparity where EP diagnosis was more pronounced among Blacks and Hispanics compared to Whites. The reason for this disparity remains unclear. Recent literature on maternal disparities suggests that the complex relationship between health outcomes and race/ethnicity may explain residual confounding in poor maternal outcomes by race.[57]

Strengths and Limitations

Strengths of this study include its population-based nature from California and the large numbers of EP. In contrast to case-control studies, which can introduce bias by selection of inappropriate controls, this retrospective cohort study included all reproductive age women who potentially were at risk for EP (e.g., if active in heterosexual sex). We used validated algorithms with high positive predictive value to ascertain EP diagnosis and contraceptive use.[58,59] Furthermore, data on exposure

measures extracted from the integrated EHRs were previously validated for epidemiological studies.[15,58-63]

Our study had limitations. EP rates are a function of pregnancy rates; an examination of pregnancy rates overall was beyond the scope of this study. We did not have information on sexual activity in the EHR, therefore we categorized contraceptive non-use time into two categories (recent contraceptive discontinuation and remote or no use) to try to identify periods when women may not have been sexually active. Also, reasons for specific contraceptive method discontinuation were not captured in the database. It is assumed that only a proportion of women who recently discontinued prescription contraceptive may have had unprotected intercourse to conceive a child. Furthermore, since data on body mass index were incomplete in the data set used, we were unable to examine its impact on our estimates. Hence, our approach may not have entirely removed the confounding effect of this and other unmeasured factors, leaving residual confounding. However, using the available data, we demonstrated that risk factor profiles for EP did not vary by maternal sociodemographic characteristics. Further research is needed to assess the contribution of maternal genetics, and anthropometric domains that were not investigated in this study.

12. Other information

12.1 Next steps

13. Conclusions

We used a combination of administrative, billing, and electronic health records to identify ectopic pregnancies among women of reproductive age from 2009 to 2018 at two large integrated health care delivery systems in California. The validation study revealed that the algorithm we used to identify ectopic pregnancies is very sensitive indicating good surveillance for the outcome of interest. Data from our health care systems demonstrates ectopic pregnancy incidence increased in the last decade and remains a significant source of reproductive health morbidity. Surgical management was utilized equally as frequent as medical treatment. Women with current contraceptive use appeared to have a lower incidence of ectopic pregnancy than the overall population of women, providing reassurance of the protective effect of contraceptives. The incidence of ectopic pregnancy was highest for women with current POP use and lowest for women with DMPA use. Factors associated with tubal factor infertility remain the most significant predictors of ectopic pregnancy.

13.1 Conclusions (AD-HOC ANALYSES)

The validation of an electronic algorithm developed to identify hormonal contraceptive use periods using EHR data for a contraception and ectopic pregnancy study showed that the algorithm is accurate and can be a useful tool for future pharmacoepidemiologic studies.

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 lower than during non-use of prescription contraceptives. After controlling for known risk

factors, EP incidence is lower among prescription contraceptive users, which could be explained partly by its action in preventing pregnancy.

Women should be counseled that use of prescription contraceptive protects from EP; women at increased risk for ectopic pregnancy who discontinue contraception should be counseled on signs and symptoms of ectopic pregnancy. The significant association observed in women of low-income or among Black and Hispanic women need further investigation and follow-up to address these disparities.

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15. Appendices

15.1 Annex 1 OS Protocol

See attached

15.2 Annex 2 OS Statistical Analysis Plan

See attached

15.3 Annex 3 Publication(s) or manuscript(s)

N/A

15.4 Annex 4 Tables and Figures

15.4.1 Table i. Scholes et al. Algorithm Diagnostic (DX) and Procedure(PX) Codes

CODE	TYPE	DESCRIPTION
633	ICD9 DX	ECTOPIC PREGNANCY
633.00		ABBDOMINAL PREGNANCY WITHOUT INTRAUTERINE PREGNANCY
633.01		ABDOMINAL PREGNANCY with INTRAUTERINE PREGNANCY
633.10		**TUBAL PREGNANCY WITHOUT INTRAUTERINE PREGNANCY**
633.11		**TUBAL PREGNANCY with INTRAUTERINE PREGNANCY**
633.20		OVARIAN PREGNANCY WITHOUT INTRAUTERINE PREGNANCY
633.21		OVARIAN PREGNANCY with INTRAUTERINE PREGNANCY
633.80		OTH ECTOPIC PG WITHOUT INTRAUTERINE PG
633.81		OTHER ECTOPIC PREGNANCY with INTRAUTERINE PREGNANCY
633.90		UNSPEC ECTOPIC PG WITHOUT INTRAUTERINE PG
633.91		UNSPEC ECTOPIC PG with INTRAUTERINE PG
58770	CPT	SALPINGOSTOMY (SALPINGONEOSTOMY)
59120		TX ECTOPIC PREGNANCY ABDOMINAL/VAGINAL APPR
59121		TX ECTOPIC PREGNANCY W/O SALPING&/OOPHORECTOMY
59130		SURGICAL TX ECTOPIC PREGNANCY; ABD PREGNANCY
59135		SURG TX ECTOPIC PG; UTERN PG RQR TOT HYSTERECT
59136		SURG TX ECTOPIC PG; UTERINE PG W/PART RES UTERUS
59140		TX ECTOPIC PREGNANCY CERVICAL W/EVACUATION
59150		LAPS TX ECTOPIC PREG W/O SALPING&/OOPHORECTOMY
59151		LAPS TX ECTOPIC PREG W/SALPING&/OOPHORECTOMY
66.62	ICD9 PX	SALPINGECTOMY WITH REMOVAL OF TUBAL PREGNANCY
74.3		REMOVAL OF EXTRATUBAL PREGNANCY
66.01		SALPINGOTOMY
66.02		SALPINGOSTOMY

*Bold font, Ectopic pregnancy specific codes (only one encounter with these codes) needed to classify a case as an ectopic pregnancy in the Scholes et al. algorithm.

15.4.2 Table ii. Enhanced Algorithm ICD-10 Diagnostic(DX) and Procedure(PX) Codes

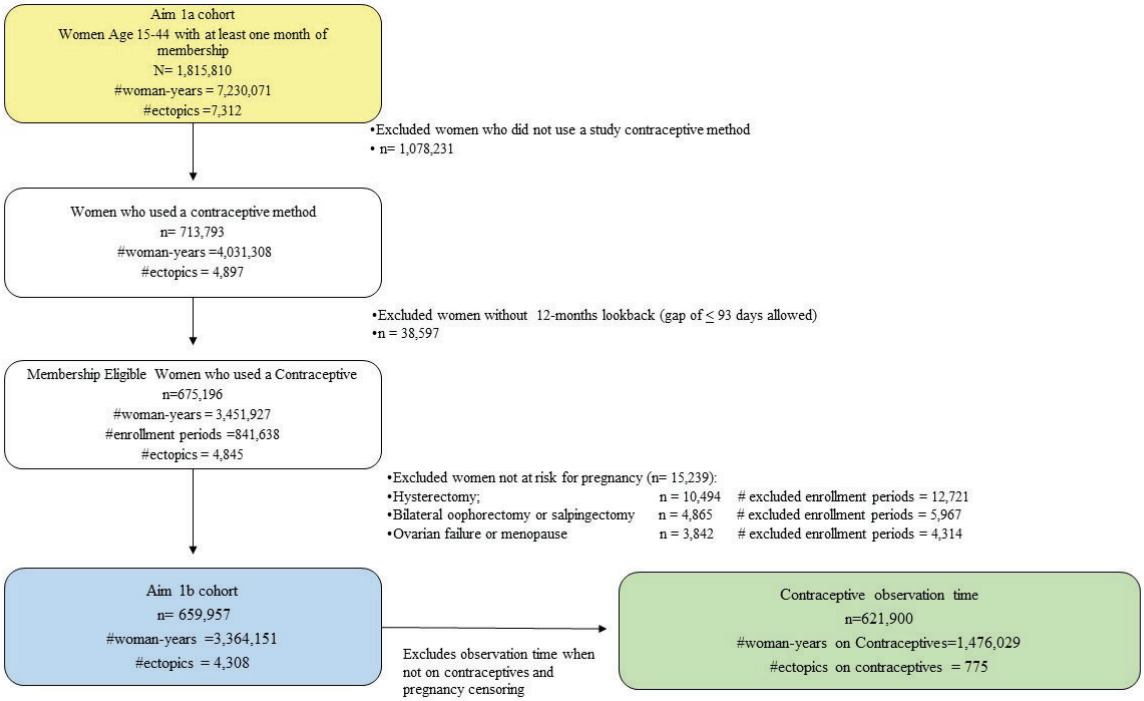
CODE	TYPE	DESCRIPTION
o00	ICD10 DX	ECTOPIC PREGNANCY
o00.00		ABDOMINAL PREGNANCY
o00.01		ABDOMINAL PREGNANCY WITHOUT INTRAUTERINE PREGNANCY
o00.01		ABDOMINAL PREGNANCY WITH INTRAUTERINE PREGNANCY
o00.1		**TUBAL PREGNANCY**
o00.10		**TUBAL PREGNANCY WITHOUT INTRAUTERINE PREGNANCY**
o00.101		**RIGHT TUBAL PREGNANCY WITHOUT INTRAUTERINE PREGNANCY**
o00.102		**LEFT TUBAL PREGNANCY WITHOUT INTRAUTERINE PREGNANCY**
o00.109		**UNSPECIFIED TUBAL PREGNANCY WITHOUT INTRAUTERINE PREGNANCY**
o00.11		**TUBAL PREGNANCY WITH INTRAUTERINE PREGNANCY**
o00.111		**RIGHT TUBAL PREGNANCY WITH INTRAUTERINE PREGNANCY**
o00.112		**LEFT TUBAL PREGNANCY WITH INTRAUTERINE PREGNANCY**
o00.119		**UNSPECIFIED TUBAL PREGNANCY WITH INTRAUTERINE PREGNANCY**
o00.2		OVARIAN PREGNANCY
o00.20		OVARIAN PREGNANCY WITHOUT INTRAUTERINE PREGNANCY
o00.201		RIGHT OVARIAN PREGNANCY WITHOUT INTRAUTERINE PREGNANCY
o00.202		LEFT OVARIAN PREGNANCY WITHOUT INTRAUTERINE PREGNANCY
o00.209		UNSPECIFIED OVARIAN PREGNANCY WITHOUT INTRAUTERINE PREGNANCY
o00.21		OVARIAN PREGNANCY WITH INTRAUTERINE PREGNANCY
o00.211		RIGHT OVARIAN PREGNANCY WITH INTRAUTERINE PREGNANCY
o00.212		LEFT OVARIAN PREGNANCY WITH INTRAUTERINE PREGNANCY
o00.219		UNSPECIFIED OVARIAN PREGNANCY WITH INTRAUTERINE PREGNANCY
o00.8		OTHER ECTOPIC PREGNANCY
o00.80		OTHER ECTOPIC PREGNANCY WITHOUT INTRAUTERINE PREGNANCY
o00.81		OTHER ECTOPIC PREGNANCY WITH INTRAUTERINE PREGNANCY
o00.9		UNSPECIFIED ECTOPIC PREGNANCY
o00.90		UNSPECIFIED ECTOPIC PREGNANCY WITHOUT INTRAUTERINE PREGNANCY
o00.91		UNSPECIFIED ECTOPIC PREGNANCY WITH INTRAUTERINE PREGNANCY
10T20ZZ	ICD10 PX	RESECTION OF PRODUCTS OF CONCEPTION, ECTOPIC, OPEN APPROACH
10T23ZZ		RESECTION OF PRODUCTS OF CONCEPTION, ECTOPIC, PERCUTANEOUS APPROACH
10T24ZZ		RESECTION OF PRODUCTS OF CONCEPTION, ECTOPIC, PERCUTANEOUS ENDOSCOPIC APPROACH
10T27ZZ		RESECTION OF PRODUCTS OF CONCEPTION, ECTOPIC, VIA NATURAL OR ARTIFICIAL OPENING
10T28ZZ		RESECTION OF PRODUCTS OF CONCEPTION, ECTOPIC, VIA NATURAL OR ARTIFICIAL OPENING ENDOSCOPIC
10D27ZZ		EXTRACTION OF PRODUCTS OF CONCEPTION, ECTOPIC, VIA NATURAL OR ARTIFICIAL OPENING
10D28ZZ		EXTRACTION OF PRODUCTS OF CONCEPTION, ECTOPIC, VIA NATURAL OR ARTIFICIAL OPENING ENDOSCOPIC

Table ii continued. Enhanced Algorithm ICD-10 Diagnostic(DX) and Procedure(PX) Codes

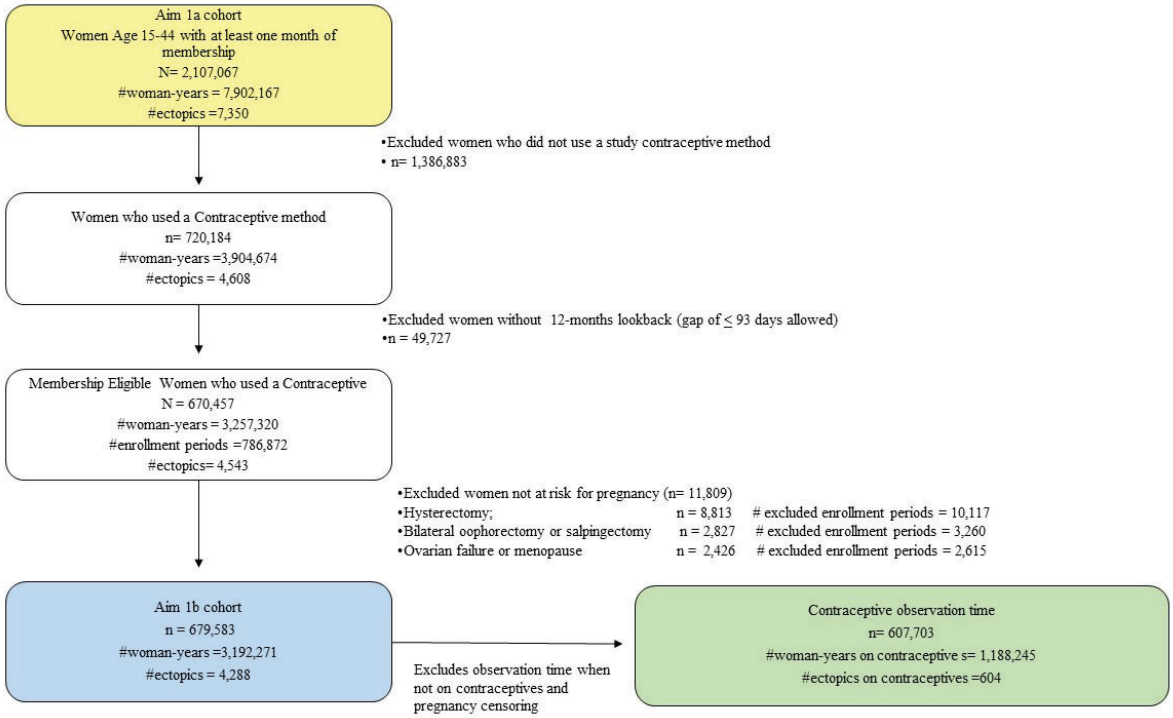
CODE	TYPE	DESCRIPTION
0UB50ZZ	ICD10 PX	EXCISION OF RIGHT FALLOPIAN TUBE, OPEN APPROACH
0UB53ZZ		EXCISION OF RIGHT FALLOPIAN TUBE, PERCUTANEOUS APPROACH
0UB54ZZ		EXCISION OF RIGHT FALLOPIAN TUBE, PERCUTANEOUS ENDOSCOPIC APPROACH
0UB57ZZ		EXCISION OF RIGHT FALLOPIAN TUBE, VIA NATURAL OR ARTIFICIAL OPENING
0UB58ZZ		EXCISION OF RIGHT FALLOPIAN TUBE, VIA NATURAL OR ARTIFICIAL OPENING ENDOSCOPIC
0UB60ZZ		EXCISION OF LEFT FALLOPIAN TUBE, OPEN APPROACH
0UB63ZZ		EXCISION OF LEFT FALLOPIAN TUBE, PERCUTANEOUS APPROACH
0UB64ZZ		EXCISION OF LEFT FALLOPIAN TUBE, PERCUTANEOUS ENDOSCOPIC APPROACH
0UB67ZZ		EXCISION OF LEFT FALLOPIAN TUBE, VIA NATURAL OR ARTIFICIAL OPENING
0UB68ZZ		EXCISION OF LEFT FALLOPIAN TUBE, VIA NATURAL OR ARTIFICIAL OPENING ENDOSCOPIC
0UT50ZZ		RESECTION OF RIGHT FALLOPIAN TUBE, OPEN APPROACH
0UT54ZZ		RESECTION OF RIGHT FALLOPIAN TUBE, PERCUTANEOUS ENDOSCOPIC APPROACH
0UT60ZZ		RESECTION OF LEFT FALLOPIAN TUBE, OPEN APPROACH
0UT64ZZ		RESECTION OF LEFT FALLOPIAN TUBE, PERCUTANEOUS ENDOSCOPIC APPROACH

***Bold font, Ectopic pregnancy specific codes (only one encounter with these codes) required to classify a case as an ectopic pregnancy in the enhanced algorithm.**

15.4.3 Figure i. Study population KPNC



15.4.4 Figure ii. Study population KPSC



15.4.5 Table iii. Ectopic Pregnancy Ascertainment - Performance of Scholes and the enhanced ectopic pregnancy algorithms (KPNC)

		Scholes Algorithm			Enhanced Algorithm		
		Yes	**No**	**Total**	**Yes**	**No**	**Total**
Chart Abstraction	**Yes**	156	4	160	159	1	160
	No	13	77	90	14	76	90
	Total	169	81	250	173	77	250
Test Characteristics	**Sensitivity**	97.5			99.4		
	Specificity	85.6			84.4		
	Negative predictive value	95.1			98.7		
	Positive predictive value	92.3			91.9		
	Youden's index	83.1			83.8		
	F-score	94.8			95.5		

15.4.6 Table iv. Ectopic Pregnancy Ascertainment - Performance of Scholes and the enhanced ectopic pregnancy algorithms (KPSC)

		Scholes Algorithm			Enhanced Algorithm		
		Yes	**No**	**Total**	**Yes**	**No**	**Total**
Chart Abstraction	**Yes**	159	15	174	167	7	174
	No	13	63	76	11	65	76
	Total	172	78	250	178	72	250
Test Characteristics	**Sensitivity**	91.4			96.0		
	Specificity	82.9			85.5		
	Negative predictive value	80.8			90.3		
	Positive predictive value	92.4			93.8		
	Youden's index	74.3			81.5		
	F-score	91.9			94.9		

15.4.7 Table v. Ectopic Pregnancy Management ascertainment – Performance of electronic data abstraction (KPNC)

		Enhanced Algorithm*			
		Surgical	**Medical**	**Unclassified**	**Total**
Chart abstraction	**Surgical**	81	3	4	88
	Medical	1	68	1	70
	Unclassified	0	1	0	1
	Total	82	72	5	159*
		Surgical v. Non-surgical			
Test Characteristics	**Sensitivity**	92.0			
	Specificity	98.6			
	Negative predictive value	90.9			
	Positive predictive value	98.8			
	Youden's index	90.6			
	F-score	95.3			
	Overall accuracy†	93.7			

* Includes cases confirmed as ectopic pregnancy by chart review and the enhanced algorithm
† The percentage of ectopic pregnancy cases with correct management (surgical, medical, and unclassified) identified by electronic chart abstraction.

15.4.8 Table vi. Ectopic Pregnancy Management ascertainment – Performance of electronic data abstraction (KPSC)

		Enhanced Algorithm cases*			
		Surgical	**Medical**	**Unclassified**	**Total**
Chart abstraction	**Surgical**	100	2	7	109
	Medical	4	50	2	56
	Unclassified	0	0	2	2
	Total	104	52	11	167*
		Surgical vs. Non-surgical			
Test Characteristics	**Sensitivity**	91.7			
	Specificity	93.1			
	Negative predictive value	85.7			
	Positive predictive value	96.2			
	Youden's index	84.8			
	F-score	93.9			
	Overall accuracy†	91.0			

* Includes cases confirmed as ectopic pregnancy by chart review and the enhanced algorithm
† The percentage of ectopic pregnancy cases with correct management (surgical, medical, and unclassified) identified by electronic chart abstraction

15.4.9 Table vii. Ectopic Pregnancy Incidence 2009 - 2018 (KPNC)

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Number of Ectopic Pregnancies*											
15-19	24	18	19	15	14	21	19	21	17	15	**183**
20-24	65	73	75	87	85	76	83	92	74	106	**816**
25-29	152	166	136	133	147	188	180	199	198	221	**1720**
30-34	179	195	217	223	214	237	261	320	283	288	**2417**
35-39	126	125	128	144	166	152	188	191	238	206	**1664**
40-44	37	44	43	51	44	51	60	54	63	65	**512**
All 15-44	583	621	618	653	670	725	791	877	873	901	**7312**
Number of Woman-Years											
15-19	110,917	110,150	112,484	112,775	111,356	111,969	115,658	118,298	118,516	120,387	**1,142,511**
20-24	89,322	87,564	99,760	105,948	107,590	113,139	119,611	123,968	127,466	130,963	**1,105,330**
25-29	101,085	98,679	101,696	103,935	104,305	112,469	124,450	135,312	145,100	152,381	**1,179,410**
30-34	107,785	109,475	112,932	116,966	119,486	127,269	138,030	146,505	153,957	161,677	**1,294,082**
35-39	112,524	110,713	110,594	112,624	114,194	121,133	131,413	140,878	150,035	158,985	**1,263,091**
40-44	114,491	114,519	116,896	118,466	118,342	122,736	127,817	131,457	137,244	143,680	**1,245,648**
All 15-44	636,123	631,099	654,363	670,714	675,273	708,714	756,978	796,417	832,317	868,072	**7,230,071**
Ectopic Pregnancy Incidence (per 10,000 Woman Years)											
Crude Rate by Age Group											
15-19	2.2	1.6	1.7	1.3	1.3	1.9	1.6	1.8	1.4	1.2	**1.6**
20-24	7.3	8.3	7.5	8.2	7.9	6.7	6.9	7.4	5.8	8.1	**7.4**
25-29	15.0	16.8	13.4	12.8	14.1	16.7	14.5	14.7	13.6	14.5	**14.6**
30-34	16.6	17.8	19.2	19.1	17.9	18.6	18.9	21.8	18.4	17.8	**18.6**
35-39	11.2	11.3	11.6	12.8	14.5	12.5	14.3	13.6	15.9	13.0	**13.1**
40-44	3.2	3.8	3.7	4.3	3.7	4.2	4.7	4.1	4.6	4.5	**4.1**
Overall Crude Rate	9.2	9.8	9.4	9.7	9.9	10.2	10.4	11.0	10.5	10.4	**10.1**
Overall Age-Adjusted Rate	9.2	9.9	9.5	9.8	9.9	10.1	10.2	10.6	10.0	9.9	**9.9**
Number of Pregnancies*											
15-19	3,070	2,807	2,688	2,334	1,822	1,668	1,587	1,453	1,300	1,165	**19,894**
20-24	6,989	6,301	6,519	6,604	6,304	6,479	6,633	6,568	6,312	6,158	**64,867**
25-29	12,149	11,777	11,361	11,349	10,797	11,376	11,827	12,569	12,644	13,034	**118,883**
30-34	12,779	12,999	13,572	14,030	14,200	15,201	16,445	17,609	17,664	17,822	**152,321**
35-39	7,658	7,517	7,701	8,112	8,155	8,723	9,358	10,026	10,821	11,228	**89,299**
40-44	2,096	2,131	2,270	2,193	2,165	2,246	2,274	2,396	2,541	2,608	**22,920**
All 15-44	44,741	43,532	44,111	44,622	43,443	45,693	48,124	50,621	51,282	52,015	**468,184**
Ectopic Pregnancy Incidence (per 1,000 Pregnancies)											
15-19	7.8	6.4	7.1	6.4	7.7	12.6	12.0	14.5	13.1	12.9	**10.0**
20-24	9.3	11.6	11.5	13.2	13.5	11.7	12.5	14.0	11.7	17.2	**12.6**
25-29	12.5	14.1	12.0	11.7	13.6	16.5	15.2	15.8	15.7	17.0	**14.4**
30-34	14.0	15.0	16.0	15.9	15.1	15.6	15.9	18.2	16.0	16.2	**15.8**
35-39	16.5	16.6	16.6	17.8	20.4	17.4	20.1	19.1	22.0	18.3	**18.5**
40-44	17.7	20.6	18.9	23.3	20.3	22.7	26.4	22.5	24.8	24.9	**22.2**
Overall Crude Rate	13.0	14.3	14.0	14.6	15.4	15.9	16.4	17.3	17.0	17.3	**15.5**
Overall Age-Adjusted Rate	13.3	14.5	14.2	14.8	15.4	15.8	16.4	17.2	16.7	17.2	**15.6**
Surgical Management											
Number	278	295	312	313	297	326	374	419	441	436	**3491**
Percent(%)	47.7	47.5	50.5	47.9	44.3	45.0	47.3	47.8	50.5	48.4	**47.7**

*Denominator includes ectopic pregnancies, live births, and abortions

15.4.10 Table viii. Ectopic Pregnancy Incidence 2009 - 2018 (KPSC)

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Number of ectopic pregnancies											
15-19	21	26	24	25	21	19	20	20	13	14	**203**
20-24	65	92	104	104	100	108	93	99	109	94	**968**
25-29	171	184	166	158	151	176	187	186	183	236	**1798**
30-34	188	185	218	192	206	202	273	247	277	277	**2265**
35-39	106	120	135	142	143	158	212	193	196	212	**1617**
40-44	36	59	43	54	37	42	50	64	63	51	**499**
All 15-44	587	666	690	675	658	705	835	809	841	884	**7350**
Number of Woman-years											
15-19	130,322	129,636	133,695	135,070	135,122	135,405	139,184	142,320	140,628	140,304	**1,361,685**
20-24	98,893	98,891	118,614	128,305	132,200	138,064	146,800	151,671	155,149	157,504	**1,326,090**
25-29	103,857	103,958	110,714	113,978	114,672	122,523	137,661	149,005	160,762	168,927	**1,286,058**
30-34	108,701	110,664	115,746	120,361	122,696	128,166	139,878	149,197	157,824	166,260	**1,319,492**
35-39	115,072	114,214	115,694	118,265	119,212	124,285	134,295	143,779	152,811	161,245	**1,298,871**
40-44	118,828	119,250	122,506	124,780	125,181	128,098	135,321	139,917	144,943	149,789	**1,308,614**
All 15-44	675,672	676,613	716,969	740,758	749,084	776,541	833,138	875,889	912,117	944,030	**7,900,810**
Ectopic Pregnancy Incidence (per 10,000 woman-years)											
Crude Rate by Age Group											
15-19	1.6	2.0	1.8	1.9	1.6	1.4	1.4	1.4	0.9	1.0	**1.5**
20-24	6.6	9.3	8.8	8.1	7.6	7.8	6.3	6.5	7.0	6.0	**7.4**
25-29	16.5	17.7	15.0	13.9	13.2	14.4	13.6	12.5	11.4	14.0	**14.2**
30-34	17.3	16.7	18.8	16.0	16.8	15.8	19.5	16.6	17.6	16.7	**17.2**
35-39	9.2	10.5	11.7	12.0	12.0	12.7	15.8	13.4	12.8	13.1	**12.3**
40-44	3.0	4.9	3.5	4.3	3.0	3.3	3.7	4.6	4.3	3.4	**3.8**
Overall Crude Rate	8.7	9.8	9.6	9.1	8.8	9.1	10.0	9.2	9.2	9.4	**9.3**
Overall Age-adjusted Rate	8.8	10.0	9.7	9.1	8.8	9.0	9.8	8.9	8.8	8.8	**9.2**
Number of pregnancies*											
15-19	2,393	3,194	2,935	2,785	2,519	2,229	2,064	1,880	1,784	1,488	**23,271**
20-24	6,155	7,653	8,398	8,695	8,709	8,729	8,791	8,788	8,299	7,457	**81,674**
25-29	10,708	12,134	12,512	12,480	12,483	12,899	13,534	14,275	14,908	13,561	**129,494**
30-34	10,439	12,084	12,993	13,580	13,954	14,660	15,541	16,567	16,683	15,798	**142,299**
35-39	5,724	6,799	6,971	7,507	7,601	7,997	8,761	9,304	9,878	9,836	**80,378**
40-44	1,368	1,851	1,854	1,995	1,901	1,953	2,110	2,239	2,270	2,336	**19,877**
All 15-44	36,787	43,715	45,663	47,042	47,167	48,467	50,801	53,053	53,822	50,476	**476,993**
EP rate per 1,000 pregnancies											
15-19	8.8	8.1	8.2	9.0	8.3	8.5	9.7	10.6	7.3	9.4	**8.8**
20-24	10.6	12.0	12.4	12.0	11.5	12.4	10.6	11.3	13.1	12.6	**11.8**
25-29	16.0	15.2	13.3	12.7	12.1	13.6	13.8	13.0	12.3	17.4	**13.9**
30-34	18.0	15.3	16.8	14.1	14.8	13.8	17.6	14.9	16.6	17.5	**15.9**
35-39	18.5	17.6	19.4	18.9	18.8	19.8	24.2	20.7	19.8	21.6	**19.9**
40-44	26.3	31.9	23.2	27.1	19.5	21.5	23.7	28.6	27.8	21.8	**25.1**
Overall Crude Rate	16.0	15.2	15.1	14.3	14.0	14.5	16.4	15.2	15.6	17.5	**15.4**
Overall Age-adjusted Rate	16.0	15.3	15.3	14.4	14.0	14.5	16.2	15.0	15.3	17.0	**15.3**
Surgical Management											
Number	303	345	381	386	354	402	479	458	472	522	
Percent (%)	**51.6**	**51.8**	**55.2**	**57.2**	**53.8**	**57.0**	**57.4**	**56.6**	**56.1**	**59.1**	**55.6**

*Denominator includes ectopic pregnancies, live births, and abortions

15.4.11 Table ix. Ectopic Pregnancy Rate by Contraceptive Method 2009 – 2018 (KPNC)

	2009-2010	2011-2012	2013-2014	2015-2016	2017-2018	All 2009-2018
Number of EP by Contraceptive Method						
Combined oral contraceptive	74	65	76	79	96	**390**
Progesting-only oral contraceptive	6	16	27	22	17	**88**
Depomedroxyprogesterone acetate	6	4	3	4	2	**19**
Levonorgestrel IUD	14	27	26	29	26	**122**
Copper IUD	6	10	13	18	16	**63**
IUD Type unknown	35	24	12	15	7	**93**
All	141	146	157	167	164	**775**
Total Woman Years						
Combined oral contraceptive	141,703	153,283	160,055	171,165	180,705	**806,911**
Progesting-only oral contraceptive	8,850	10,512	12,461	15,187	15,329	**62,340**
Depomedroxyprogesterone acetate	14,937	16,334	17,243	16,930	17,441	**82,886**
Levonorgestrel IUD	26,948	56,578	72,393	81,790	90,973	**328,682**
Copper IUD	6,503	13,729	18,547	21,646	23,913	**84,338**
IUD Type unknown	31,955	21,301	18,903	20,521	18,193	**110,873**
All	230,897	271,738	299,602	327,238	346,555	**1,476,029**
EP Rate per 10,000 years of observation time						
Combined oral contraceptive	5.2	4.2	4.7	4.6	5.3	**4.8**
Progesting-only oral contraceptive	6.8	15.2	21.7	14.5	11.1	**14.1**
Depomedroxyprogesterone acetate	4.0	2.4	1.7	2.4	1.1	**2.3**
Levonorgestrel IUD	5.2	4.8	3.6	3.5	2.9	**3.7**
Copper IUD	9.2	7.3	7.0	8.3	6.7	**7.5**
IUD Type unknown	11.0	11.3	6.3	7.3	3.8	**8.4**
Overall Crude Rate	**6.1**	**5.4**	**5.2**	**5.1**	**4.7**	**5.3**
Overall Adjusted Rate	**5.8**	**5.4**	**5.2**	**5.0**	**4.7**	**5.2**

15.4.12 Table x. Ectopic Pregnancy Rate by Contraceptive Method 2009 – 2018 (KPSC)

	2009-2010	2011-2012	2013-2014	2015-2016	2017-2018	All 2009-2018
Number of EP by Contraceptive Method						
Combined oral contraceptive	60	59	58	69	90	**336**
Progesting-only oral contraceptive	10	9	7	18	18	**62**
Depomedroxyprogesterone acetate	4	5	8	3	2	**22**
Levonorgestrel IUD	4	20	11	13	13	**61**
Copper IUD	1	10	9	2	14	**36**
IUD Type unknown	33	21	5	16	12	**87**
All	112	124	98	121	149	**604**
Total Woman Years						
Combined oral contraceptive	113137	134501	143324	161334	169798	**722,094**
Progesting-only oral contraceptive	5119	6339	7597	9556	10663	**39,273**
Depomedroxyprogesterone acetate	11192	13257	14420	14761	14688	**68,317**
Levonorgestrel IUD	15617	35102	44897	51360	60560	**207,537**
Copper IUD	4362	10130	13359	15295	17165	**60,311**
IUD Type unknown	22674	18158	18043	17906	13933	**90,714**
All	172,100	217,487	241,639	270,212	286,807	**1,188,245**
EP Rate per 10,000 years of observation time						
Combined oral contraceptive	5.3	4.4	4.0	4.3	5.3	**4.7**
Progesting-only oral contraceptive	19.5	14.2	9.2	18.8	16.9	**15.8**
Depomedroxyprogesterone acetate	3.6	3.8	5.5	2.0	1.4	**3.2**
Levonorgestrel IUD	2.6	5.7	2.5	2.5	2.1	**2.9**
Copper IUD	2.3	9.9	6.7	1.3	8.2	**6.0**
IUD Type unknown	14.6	11.6	2.8	8.9	8.6	**9.6**
Overall Crude Rate	**6.5**	**5.7**	**4.1**	**4.5**	**5.2**	**5.1**
Overall Adjusted Rate	**5.7**	**5.7**	**4.1**	**4.5**	**5.2**	**5.0**

15.4.13 Table xi. Characteristics of Women with Current Contraceptive Use* (KPNC)

Characteristics	Contraceptive methods				†*P*-value
	Combined OCP N = 396,454 (63.7)	**Progestin-only OCP N = 47,098 (7.6)**	**DMPA N = 48,469 (7.8)**	**IUDs N = 129,879 (20.9)**	
	n(%)	n(%)	n(%)	n(%)	
Age, year					<.0001
15-19	105,947 (26.7)	1,681 (3.6)	15,375 (31.7)	8,827 (6.8)	
20-29	171,269 (43.2)	17,791 (37.8)	18,198 (37.5)	47,079 (36.2)	
30-34	57,662 (14.5)	14,829 (31.5)	6,690 (13.8)	32,287 (24.9)	
≥35	61,576 (15.5)	12,797 (27.2)	8,206 (16.9)	41,686 (32.1)	
Race/Ethnicity					<.0001
Non-Hispanic White	188,685 (47.6)	20,726 (44)	15,430 (31.8)	54,527 (42.0)	
Non-Hispanic Black	26,367 (6.7)	3,457 (7.3)	8,170 (16.9)	10,441 (8.0)	
Hispanic	82,911 (20.9)	11,456 (24.3)	16,175 (33.4)	35,990 (27.7)	
Asian/Pacific Islander	76,682 (19.3)	10,239 (21.7)	6,702 (13.8)	23,805 (18.3)	
Other/Unknown	21,809 (5.5)	1,220 (2.6)	1,992 (4.1)	5,116 (3.9)	
Smoking[a]					<.0001
Never	257,584 (65.0)	35,923 (76.3)	29,988 (61.9)	86,473 (66.6)	
Former	22,374 (5.6)	5,251 (11.1)	3,152 (6.5)	12,052 (9.3)	
Current	21,288 (5.4)	3,380 (7.2)	5,598 (11.5)	10,971 (8.4)	
Missing	95,208 (24.0)	2,544 (5.4)	9,731 (20.1)	20,383 (15.7)	
Parity					<.0001
Nullipara	135,357 (34.1)	10,793 (22.9)	10,496 (21.7)	22,833 (17.6)	
Multipara	74,532 (18.8)	29,941 (63.6)	17,758 (36.6)	75,473 (58.1)	
Missing	186,565 (47.1)	6,364 (13.5)	20,215 (41.7)	31,573 (24.3)	
Median household Income[b]**, USD**					<.0001
< $30,000	13,959 (3.5)	1,573 (3.3)	3,037 (6.3)	5,386 (4.1)	
$30,000-$49,999	65,837 (16.6)	7,988 (17.0)	12,013 (24.8)	23,881 (18.4)	
$50,000-$69,999	99,004 (25.0)	11,840 (25.1)	13,661 (28.2)	33,112 (25.5)	
$70,000-$89,999	91,266 (23.0)	10,851 (23.0)	10,086 (20.8)	29,112 (22.4)	
≥ $90,000	126,096 (31.8)	14,833 (31.5)	9,642 (19.9)	38,322 (29.5)	
Missing	292 (0.1)	13 (0)	30 (0.1)	66 (0.1)	

Abbreviations: OCP, Oral Contraceptive Pills; DMPA, Depomedroxyprogesterone acetate; USD, United States Dollar; IUD, levonorgestrel or copper IUD; †P-values for characteristic-specific differences in contraceptive method use.

[a] Smoking status documented in the year prior to the index date.

[b] Median family household income based on census tract of residence

15.4.14 Table xii. Incidence Rates per 10,000 woman-years and Risk of Ectopic Pregnancy (crude and adjusted hazard ratios) Associated with demographic characteristics (KPNC)

Characteristics	Total Woman-years	EP (N)	Incidence rate[a]	Hazard Ratio (95% Confidence Intervals)		*P*-value
				Crude	Adjusted[b]	
Total	1,476,029	775	5.25	--	--	--
Age, year						
15-19	166,614	37	2.22	0.37 (0.26, 0.52)	0.52 (0.36, 0.75)	0.0005
20-29	566,100	340	6.01	1.00 (reference)	1.00 (reference)	
30-34	296,683	222	7.48	1.26 (1.06, 1.49)	0.90 (0.75, 1.07)	0.2333
≥35	446,633	176	3.94	0.68 (0.56, 0.81)	0.45 (0.37, 0.55)	< 0.0001
Race/Ethnicity						
Non-Hispanic White	725,088	310	4.28	1.00 (reference)	1.00 (reference)	
Non-Hispanic Black	101,969	107	10.49	2.46 (1.98, 3.07)	1.92 (1.52, 2.41)	< 0.0001
Hispanic	328,070	239	7.29	1.71 (1.44, 2.02)	1.39 (1.16, 1.65)	0.0003
Asian/Pacific Islander	268,573	105	3.91	0.92 (0.74, 1.15)	0.84 (0.67, 1.05)	0.1218
Other/Unknown	52,330	14	2.68	0.61 (0.36, 1.05)	0.65 (0.38, 1.11)	0.1177
Smoking						
Never	984,119	518	5.26	1.00 (reference)	1.00 (reference)	
Former	129,464	85	6.57	1.26 (1.00, 1.58)	1.15 (0.92, 1.45)	0.2248
Current	87,367	88	10.07	1.89 (1.51, 2.37)	1.81 (1.44, 2.28)	< 0.0001
Missing	275,079	84	3.05	0.58 (0.46, 0.72)	0.69 (0.54, 0.87)	0.0017
Parity						
Nullipara	537,837	186	3.46	1.00 (reference)	1.00 (reference)	
Multipara	654,473	500	7.64	2.25 (1.90, 2.67)	2.69 (2.20, 3.28)	< 0.0001
Missing	283,719	89	3.14	0.86 (0.67, 1.11)	1.09 (0.84, 1.42)	0.5275
Median household income[c], USD						
< $30,000	47,466	40	8.43	2.10 (1.49, 2.95)	1.56 (1.10, 2.22)	0.0117
$30,000-$49,999	238,139	153	6.42	1.60 (1.30, 1.99)	1.27 (1.02, 1.58)	0.0334
$50,000-$69,999	368,583	205	5.56	1.39 (1.14, 1.70)	1.21 (0.99, 1.48)	0.0609
$70,000-$89,999	342,104	186	5.44	1.36 (1.11, 1.67)	1.24 (1.02, 1.52)	0.0345
≥ $90,000	479,102	191	3.99	1.00 (reference)	1.00 (reference)	
Missing	635	0	--	--	--	--

Abbreviations: KPNC, Kaiser Permanente Northern California; EP, ectopic pregnancy; USD, United States Dollar

[a]Incidence rate is shown per 10,000 Woman-years.

[b]Hazard ratios were adjusted for covariates listed in this table and that of Table xiii

[c]Median family household income based on census tract of residence

15.4.15 Table xiii. Incidence Rates per 10,000 woman-years and Risk of Ectopic Pregnancy (crude and adjusted hazard ratios) associated with potential medical, obstetrical, and contraceptive risk factors (KPNC)

Potential risk factors	Total Woman-years	EP (N)	Incidence rate[a]	Hazard Ratio (95% Confidence Intervals)		*P*-value
				Crude	Adjusted[b]	
History of ectopic pregnancy						
No	1,472,427	756	5.13	1.00 (ref.)	1.00 (ref.)	
Yes	3,602	19	52.74	10.80 (6.83, 17.06)	5.31 (3.25, 8.68)	<0.0001
History of STD						
No	1,414,488	697	4.93	1.00 (ref.)	1.00 (ref.)	
Yes	61,542	78	12.67	2.69 (2.12, 3.41)	2.00 (1.55, 2.57)	< 0.0001
History of PID (2 or more diagnoses)						
No	1,472,251	762	5.18	1.00 (ref.)	1.00 (ref.)	
Yes	3,778	13	34.41	6.86 (3.96, 11.87)	3.67 (2.10, 6.42)	< 0.0001
History of infertility						
No	1,444,829	705	4.88	1.00 (ref.)	1.00 (ref.)	
Yes	31,200	70	22.44	4.89 (3.81, 6.27)	3.93 (3.02, 5.13)	< 0.0001
History of endometriosis						
No	1,395,614	721	5.17	1.00 (ref.)	1.00 (ref.)	
Yes	80,416	54	6.72	1.34 (1.02, 1.77)	0.96 (0.72, 1.27)	0.7683
History of congenital malformation						
No	1,472,077	773	5.25	1.00 (ref.)	1.00 (ref.)	
Yes	3,952	2	5.06	0.99 (0.25, 3.96)	0.48 (0.12, 1.93)	0.2990
History of pelvic organ surgeries						
Cesarean section						
No	1,376,000	691	5.02	1.00 (ref.)	1.00 (ref.)	
Yes	100,029	84	8.40	1.74 (1.38, 2.18)	0.94 (0.74, 1.20)	0.6316
Tubal ligation/occlusion						
No	1,469,890	772	5.25	1.00 (ref.)	1.00 (ref.)	
Yes	6,140	3	4.89	0.96 (0.31, 2.99)	0.65 (0.21, 2.02)	0.4536
Myomectomy						
No	1,471,238	765	5.20	1.00 (ref.)	1.00 (ref.)	
Yes	4,792	10	20.87	4.16 (2.23, 7.77)	2.69 (1.40, 5.18)	0.0031
Adnexal surgery						
No	1,465,205	758	5.17	1.00 (ref.)	1.00 (ref.)	
Yes	10,824	17	15.71	3.14 (1.94, 5.09)	1.21 (0.71, 2.07)	0.4814
Appendectomy						
No	1,461,241	770	5.27	1.00 (ref.)	1.00 (ref.)	
Yes	14,788	5	3.38	0.66 (0.28, 1.60)	0.59 (0.24, 1.42)	0.2392
Any pelvic surgery						
No	1,348,222	665	4.93	1.00 (ref.)	1.00 (ref.)	
Yes	127,808	110	8.61	1.82 (1.48, 2.23)	1.02 (0.82, 1.27)	0.8469

Table xiii. continued. Incidence Rates per 10,000 woman-years and Risk of Ectopic Pregnancy (crude and adjusted hazard ratios) associated with potential medical, obstetrical, and contraceptive risk factors (KPNC)

Potential risk factors	Total Woman-years	EP (N)	Incidence rate[a]	Hazard Ratio (95% Confidence Intervals)		*P*-value
				Crude	Adjusted	
Contraceptive method						
DMPA	82,886	19	2.29	1.00 (Ref.)	1.00 (Ref.)	
Combined OCP use	806,911	390	4.83	2.10 (1.32, 3.32)	3.52 (2.21, 5.62)	< 0.0001
Progestin-only OCP use	62,340	88	14.12	6.16 (3.75, 10.11)	5.77 (3.49, 9.54)	< 0.0001
Intrauterine device (IUD)	523,893	278	5.31	2.34 (1.47, 3.73)	2.50 (1.56, 3.99)	< 0.0001
Levonorgestrel IUD	328,682	122	3.71	1.64 (1.01, 2.66)	1.68 (1.03, 2.73)	0.0372
Copper-containing IUD	84,338	63	7.47	3.29 (1.97, 5.51)	3.52 (2.10, 5.92)	< 0.0001
Unknown IUD type	110,873	93	8.39	3.55 (2.16, 5.82)	4.32 (2.62, 7.12)	< 0.0001

Abbreviations: KPNC, Kaiser Permanente Northern California; EP, ectopic pregnancy; PID, pelvic inflammatory disease; STD, sexual transmitted disease limited to chlamydia and/or gonorrhea infection; DMPA, Depomedroxyprogesterone acetate; OCP, Oral contraceptive Pills.
[a]Incidence rate is shown per 10,000 Woman-years.
[b]Hazard ratios were adjusted for factors listed in Tables xii. and xiii.

15.4.16 Table xiv. Characteristics of Women with Current Contraceptive Use (KPSC)

Characteristics	Contraceptive methods				†*P*-value
	Combined OCP N = 404,464 (66.6)	**Progestin-only OCP N = 43,883 (7.2)**	**DMPA N = 58,395 (9.6)**	**IUDs N = 100,961 (16.6)**	
	n(%)	n(%)	n(%)	n(%)	
Age, year					<.0001
15-19	94,243 (23.3)	1,633 (3.7)	15,753 (27.0)	6,310 (6.2)	
20-29	185,359 (45.8)	19,120 (43.6)	24,124 (41.3)	41,498 (41.1)	
30-34	59,315 (14.7)	13,803 (31.5)	8,682 (14.9)	23,983 (23.8)	
≥35	65,547 (16.2)	9,327 (21.3)	9,836 (16.8)	29,170 (28.9)	
Race/Ethnicity					<.0001
Non-Hispanic White	142,251 (35.2)	14,573 (33.2)	11,767 (20.2)	27,505 (27.2)	
Non-Hispanic Black	30,662 (7.6)	3,013 (6.9)	9,111 (15.6)	8,636 (8.6)	
Hispanic	163,996 (40.5)	19,724 (44.9)	31,995 (54.8)	53,057 (52.6)	
Asian/Pacific Islander	41,884 (10.4)	5,491 (12.5)	3,386 (5.8)	8,170 (8.1)	
Other/Unknown	25,671 (6.3)	1,082 (2.5)	2,136 (3.7)	3,593 (3.6)	
Smoking Status[a]					<.0001
Never	297,062 (73.4)	35,854 (81.7)	42,221 (72.3)	74,430 (73.7)	
Former	22,969 (5.7)	4,762 (10.9)	4,331 (7.4)	9,197 (9.1)	
Current	21,617 (5.3)	2,257 (5.1)	5,278 (9.0)	7,519 (7.4)	
Missing	62,816 (15.5)	1,010 (2.3)	6,565 (11.2)	9,815 (9.7)	
Parity					<.0001
Nullipara	103,879 (25.7)	7,681 (17.5)	10,076 (17.3)	11,844 (11.7)	
Multipara	84,013 (20.8)	30,883 (70.4)	25,349 (43.4)	65,597 (65.0)	
Missing	216,572 (53.5)	5,319 (12.1)	22,970 (39.3)	23,520 (23.3)	
Median household income[b]**, USD**					<.0001
< $30,000	15,474 (3.8)	1,677 (3.8)	4,007 (6.9)	5,218 (5.2)	
$30,000-$49,999	91,423 (22.6)	10,295 (23.5)	18,639 (31.9)	28,085 (27.8)	
$50,000-$69,999	114,487 (28.3)	12,522 (28.5)	17,804 (30.5)	29,663 (29.4)	
$70,000-$89,999	88,510 (21.9)	9,565 (21.8)	10,523 (18.0)	20,030 (19.8)	
≥ $90,000	93,598 (23.1)	9,711 (22.1)	7,352 (12.6)	17,799 (17.6)	
Missing	972 (0.2)	113 (0.3)	70 (0.1)	166 (0.2)	

Abbreviations: OCP, Oral Contraceptive Pills; DMPA, Depomedroxyprogesterone acetate; USD, United States Dollar; IUD, levonorgestrel or copper IUD
†P-values for characteristic-specific differences in contraceptive method use.
[a] Smoking status documented within year prior to the index date.
[b]Median family household income based on census tract of residence

15.4.17 Table xv. Incidence Rates per 10,000 woman-years and Risk of Ectopic Pregnancy (crude and adjusted hazard ratios) Associated with demographic characteristics (KPSC)

Characteristics	Total Woman-years	EP (N)	Incidence rate[a]	Hazard Ratio (95% Confidence Intervals)		*P*-value
				Crude	Adjusted[b]	
Total	1,188,245	604	5.08	--	--	--
Age, year						
15-19	122,619	22	1.79	0.33 (0.22, 0.52)	0.43 (0.28, 0.68)	0.0003
20-29	497,857	256	5.14	1.00 (reference)	1.00 (reference)	
30-34	236,882	184	7.77	1.52 (1.25, 1.83)	0.11 (0.92, 1.38)	0.2500
≥35	330,887	142	4.29	0.85 (0.69, 1.04)	0.60 (0.48, 0.76)	< 0.0001
Race/Ethnicity						
Non-Hispanic White	420,452	139	3.31	1.00 (reference)	1.00 (reference)	
Non-Hispanic Black	95,732	74	7.73	2.37 (1.78, 3.14)	2.11 (1.58, 2.84)	< 0.0001
Hispanic	512,674	331	6.46	1.97 (1.62, 2.40)	1.70 (1.38, 2.09)	< 0.0001
Asian/Pacific Islander	114,181	47	4.12	1.25 (0.90, 1.74)	1.13 (0.81, 1.58)	0.4673
Other/Unknown	45,207	13	2.88	0.84 (0.47, 1.48)	0.91 (0.52, 1.61)	0.7488
Smoking Status						
Never	882,037	450	5.10	1.00 (reference)	1.00 (reference)	
Former	100,382	56	5.58	1.10 (0.84, 1.46)	1.06 (0.80, 1.40)	0.6723
Current	61,111	45	7.36	1.43 (1.05, 1.94)	1.58 (1.16, 2.15)	0.0039
Missing	144,715	53	3.66	0.72 (0.54, 0.96)	0.82 (0.62, 1.10)	0.1854
Parity						
Nullipara	336,638	134	3.98	1.00 (reference)	1.00 (reference)	
Multipara	532,436	370	6.95	1.77 (1.45, 2.15)	1.75 (1.39, 2.21)	< 0.0001
Missing	319,171	100	3.13	0.74 (0.57, 0.96)	0.88 (0.67, 1.14)	0.3353
Median household income[c], USD						
< $30,000	48,091	36	7.49	2.13 (1.45, 3.16)	1.46 (0.99, 2.17)	0.0585
$30,000-$49,999	275,696	162	5.88	1.66 (1.29, 2.15)	1.21 (0.93, 1.57)	0.1663
$50,000-$69,999	340,891	203	5.95	1.69 (1.32, 2.16)	1.34 (1.04, 1.72)	0.0220
$70,000-$89,999	259,069	109	4.21	1.19 (0.90, 1.57)	1.04 (0.78, 1.37)	0.7987
≥ $90,000	263,021	93	3.54	1.00 (reference)	1.00 (reference)	
Missing	1,478	1	6.76	1.79 (0.25, 12.86)	1.84 (0.26, 13.19)	0.5463

Abbreviations: KPNC, Kaiser Permanente Northern California; EP, ectopic pregnancy; USD, United States Dollar

[a]Incidence rate is shown per 10,000 Woman-years.

[b]Hazard ratios were adjusted for covariates listed in this table and that of Table xvi

[c]Median family of household income based on census tract of residence

15.4.18 Table xvi. Incidence Rates per 10,000 woman-years and Risk of Ectopic Pregnancy (crude and adjusted hazard ratios) associated with potential medical, obstetrical, and contraceptive risk factors (KPSC)

Potential risk factors	Total Woman-years	EP (N)	Incidence rate[a]	Hazard Ratio (95% Confidence Intervals)		*P*-value
				Crude	Adjusted[b]	
History of ectopic pregnancy						
No	1,185,040	594	5.01	1.00 (ref.)	1.00 (ref.)	
Yes	3,206	10	31.19	6.42 (3.43, 12.02)	2.84 (1.40, 5.74)	0.0038
History of STD						
No	1,120,344	561	5.01	1.00 (ref.)	1.00 (ref.)	
Yes	67,902	43	6.33	1.31 (0.96, 1.78)	1.13 (0.82, 1.56)	0.4661
History of PID (2 or more diagnoses)						
No	1,185,313	600	5.06	1.00 (ref.)	1.00 (ref.)	
Yes	2,932	4	13.64	2.76 (1.03, 7.39)	1.52 (0.56, 4.14)	0.4099
History of infertility						
No	1,164,096	530	4.55	1.00 (ref.)	1.00 (ref.)	
Yes	24,150	74	30.64	7.17 (5.59, 9.18)	5.98 (4.60, 7.77)	< 0.0001
History of endometriosis						
No	1,144,677	577	5.04	1.00 (ref.)	1.00 (ref.)	
Yes	43,568	27	6.20	1.25 (0.85, 1.84)	0.84 (0.56, 1.25)	0.3919
History of congenital malformation						
No	1,185,159	601	5.07	1.00 (ref.)	1.00 (ref.)	
Yes	3,086	3	9.72	1.95 (0.63, 6.06)	1.05 (0.33, 3.28)	0.9374
History of pelvic organ surgeries						
Cesarean section						
No	1,095,726	543	4.96	1.00 (ref.)	1.00 (ref.)	
Yes	92,520	61	6.59	1.37 (1.05, 1.79)	0.78 (0.59, 1.04)	0.0884
Tubal ligation/occlusion						
No	1,181,139	601	5.09	1.00 (ref.)	1.00 (ref.)	
Yes	7,107	3	4.22	0.85 (0.27, 2.65)	0.65 (0.21, 2.04)	0.4623
Myomectomy						
No	1,183,724	597	5.04	1.00 (ref.)	1.00 (ref.)	
Yes	4,521	7	15.48	3.17 (1.50, 6.68)	1.78 (0.82, 3.87)	0.1438
Adnexal surgery						
No	1,176,908	587	4.99	1.00 (ref.)	1.00 (ref.)	
Yes	11,337	17	14.99	3.10 (1.91, 5.03)	1.40 (0.79, 2.48)	0.2427
Appendectomy						
No	1,176,619	594	5.05	1.00 (ref.)	1.00 (ref.)	
Yes	11,627	10	8.60	1.75 (0.94, 3.28)	1.70 (0.91, 3.19)	0.0981
Any pelvic surgery						
No	1,069,719	509	4.76	1.00 (ref.)	1.00 (ref.)	
Yes	118,527	95	8.02	1.75 (1.40, 2.19)	1.04 (0.82, 1.33)	0.7219

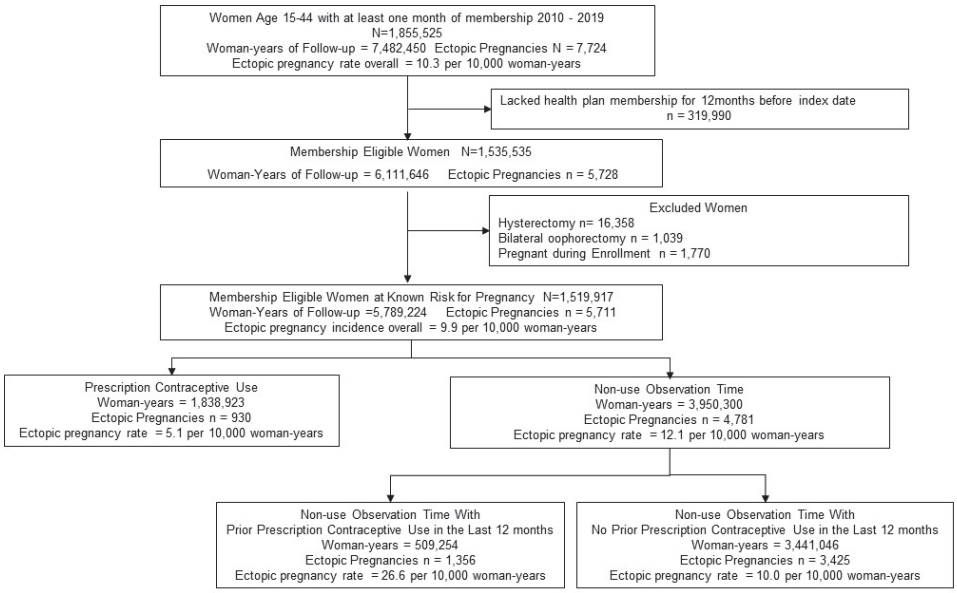
15.4.19 Table xvi continued. Incidence Rates per 10,000 woman-years and Risk of Ectopic Pregnancy (crude and adjusted hazard ratios) associated with potential medical, obstetrical, and contraceptive risk factors (KPSC)

Potential risk factors	Total Woman-years	EP (N)	Incidence rate[a]	Hazard Ratio (95% Confidence Intervals)		*P*-value
				Crude	Adjusted[b]	
Contraceptive method						
DMPA	68,317	22	3.22	1.00 (Ref.)	1.00 (Ref.)	
Combined OCP use	722,094	336	4.65	1.44 (0.93, 2.21)	1.99 (1.29, 3.09)	0.0020
Progestin-only OCP use	39,273	62	15.79	4.91 (3.02, 7.98)	4.04 (2.47, 6.62)	< 0.0001
Intrauterine device (IUD)	358,561	184	5.13	1.62 (1.04, 2.52)	1.53 (0.98, 2.40)	0.0600
Levonorgestrel IUD	207,537	61	2.94	0.91 (0.56, 1.49)	0.84 (0.52, 1.38)	0.4956
Copper-containing IUD	60,311	36	5.97	1.86 (1.09, 3.17)	1.77 (1.04, 3.03)	0.0361
Unknown IUD type	90,714	87	9.59	2.92 (1.83, 4.67)	2.98 (1.86, 4.79)	< 0.0001

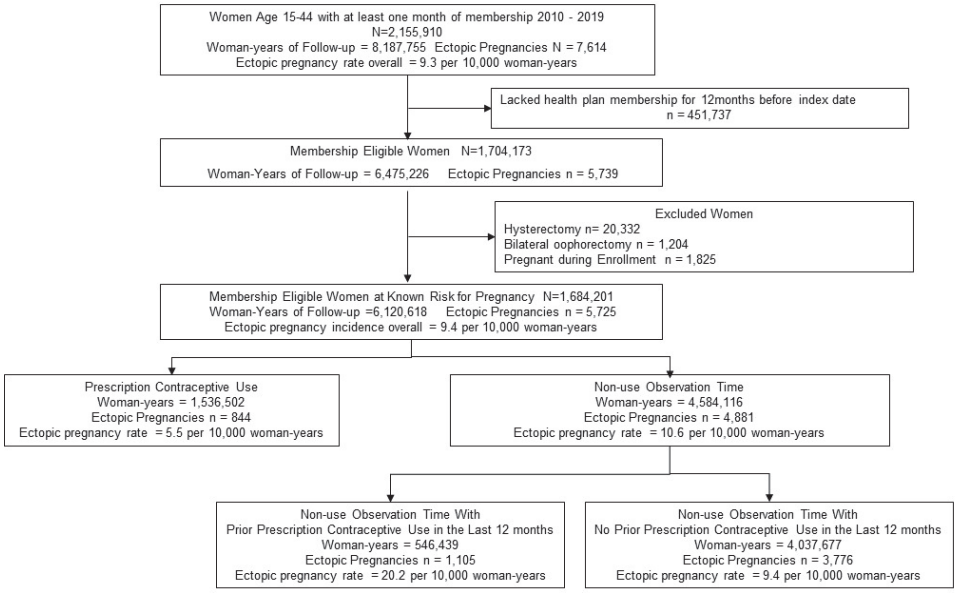
Abbreviations: KPNC, Kaiser Permanente Northern California; EP, ectopic pregnancy; PID, pelvic inflammatory disease; STD, sexual transmitted disease limited to chlamydia and/or gonorrhea infection; DMPA, Depomedroxyprogesterone acetate; OCP, Oral contraceptive Pills.
[a]Incidence rate is shown per 10,000 Woman-years.
[b]Hazard ratios were adjusted for factors listed in Tables xv. and xvi.

15.5 Appendices (Post-hoc analyses)

15.5.1 Figure iii. Ectopic Pregnancy Incidence in Women with Prescription Contraceptive Use and Non-use 2010 – 2019 (KPNC)



15.5.2 Figure iv. Ectopic Pregnancy Incidence in Women with Prescription Contraceptive Use and Non-use 2010 – 2019 (KPSC)



15.5.3 Table xvii. Demographics of the Study Population by Prescription Contraceptive Use 2010 to 2019; Kaiser Permanente Northern California - N = 1,519,917

	Total	Only Used Combined Hormonal Contraceptives[1]	Only Used Intrauterine Devices	Only Used DMPA	Only Used Progesterone-only Pill	Only Used Implant	Used More Than One Method	No Methods Used
	N = 1,519,917 (%)	n = 771,332 (50.8)	n = 206,394 (13.6)	n = 330,726 (21.8)	n = 137,123 (9.0)	n = 27,843 (1.8)	n = 22,635 (1.5)	n = 23,864 (1.6)
Woman-years Mean ± SD	3.8 ± 2.9	2.9 ±2.6	5.9 ± 2.6	4.4 ± 3.0	4.4 ± 2.9	4.1 ± 2.8	3.8 ± 2.9	3.6 ± 2.6
Time on method (years) mean ± SD	2.7 ± 2.5	2.9 ± 2.6	3.5 ± 2.3	1.9 ± 2.1	3.0 ± 2.5	1.4 ± 1.8	0.6 ± 0.9	1.8 ± 1.6
Age at Method start (years) mean± SD	28.2 ± 8.9	28.9 ± 9.8	25.9 ± 7.1	26.9 ± 8.0	31.6 ± 7.0	27.2 ± 8.6	32.6 ± 6.4	23.6 ± 6.8
15-19	22.7	56.5	14.5	22.1	2.1	2.1	0.2	2.5
20-29	32.1	38.2	18.5	28.5	9.4	2.0	1.4	2.2
30-34	17.0	47.4	15.1	19.2	13.2	1.6	2.6	1.0
≥ 35	28.2	62.5	6.4	15.4	11.7	1.6	2.0	0.5
Race/Ethnicity								
Non-Hispanic White	37.8	31.5	45.1	46.4	43.0	31.3	42.3	32.2
Non-Hispanic Black	7.1	6.7	8.7	5.7	7.1	16.3	7.6	9.8
Hispanic	23.6	23.0	26.5	20.4	26.2	33.6	23.3	37.8
Asian/Pacific Islander	21.4	24.8	15.1	19.9	18.2	13.0	22.2	13.8
Other/Unknown	10.2	14.0	4.7	7.6	5.6	5.9	4.5	6.4
Income[2], US Dollars								
< $30,000	14.3	4.6	3.9	3.6	4.2	6.6	3.9	6.0
$30,000-$49,999	18.4	18.8	18.3	16.5	18.5	25.4	17.9	4.2
$50,000-$69,999	25.1	24.8	26.1	24.7	25.4	28.3	25.5	27.8
$70,000-$89,999	22.4	22.1	22.9	23.0	22.2	20.4	23.2	20.5
≥ $90,000	29.7	29.5	28.7	32.2	29.6	19.2	29.5	21.7
Missing	0.2	0.2	0	0.1	0.1	0	0	0.2

15.5.4 Table xviii. Demographics of the Study Population by Prescription Contraceptive Use 2010 to 2019 (KPSC)

	Total	Only Used Combined Hormonal Contraceptives[1]	Only Used Intrauterine Devices	Only Used DMPA	Only Used Progesterone-only Pill	Only Used Implant	Used More Than One Method	No Methods Used
	N=1,684,201 (%)	949,241 (56.4%)	172,100 (10.2%)	386,729 (23.0%)	99,546 (5.9%)	33,644 (2.0%)	22,985 (1.4%)	19,956 (1.2%)
Woman-years Mean ± SD	3.6 ± 2.9	2.9 ± 2.6	5.8 ± 2.6	4.3 ± 2.9	4.4 ± 2.9	4.1 ± 2.8	3.6 ± 2.8	3.4 ± 2.5
Time on method (years) mean ± SD	2.5 ± 2.4	2.9 ± 2.6	3.0 ± 2.2	1.7 ± 1.9	2.7 ± 2.4	0.9 ± 1.2	0.6 ± 0.9	1.7 ± 1.5
Age at Method start (years) mean± SD	28.3 ± 8.7	28.9 ± 9.4	26.2 ± 6.8	27.0 ± 7.7	31.1 ± 7.0	27.3 ± 8.1	31.1 ± 6.0	24.3 ± 6.2
15-19	22.1	25.1	20.9	20.4	5.0	22.4	3.0	26.0
20-29	34.0	26.0	47.6	45.1	37.3	38.8	37.4	55.0
30-34	16.2	15.2	18.7	15.2	23.6	16.0	31.0	11.6
≥ 35	27.7	33.8	12.9	19.3	34.1	22.7	28.7	7.3
Race/Ethnicity								
Non-Hispanic White	27.1	23.6	29.4	35.2	28.7	19.7	32.8	20.9
Non-Hispanic Black	7.8	7.4	9.9	7.2	7.9	15.7	6.8	7.8
Hispanic	44.2	43.6	50.2	39.8	50.4	54.4	43.2	59.0
Asian/Pacific Islander	11.3	12.6	7.9	11.1	8.7	6.1	14.1	6.5
Other/Unknown	9.5	12.8	2.6	6.8	4.3	4.1	3.1	5.8
Income[2], US Dollars								
< $30,000	4.4	4.5	4.7	3.6	4.6	6.9	3.5	5.3
$30,000-$49,999	24.8	25.7	25.6	21.4	26.1	31.5	22.6	29.2
$50,000-$69,999	28.2	28.2	29.1	27.5	28.3	30.3	27.3	29.3
$70,000-$89,999	20.9	20.4	21.1	22.3	20.6	18.2	21.9	19.8
≥ $90,000	21.5	20.8	19.5	25.0	20.2	13.0	24.4	16.2
Missing	0.3	0.3	0.1	0.3	0.2	0.2	0.3	0.3

15.5.5 Table xix. Ectopic Pregnancy Incidence by Prescription Contraceptive Method 2010-2019 (KPNC) - N = 1,519,917

Method	Number of Ectopic Pregnancies	Woman-years	Incidence per 10,000 woman years	95% Confidence Interval
Combined Hormonal Contraceptive	451	920,352	4.9	4.5-5.4
Levonorgestrel IUD	180	478,183	3.8	3.3-4.4
Copper IUD	119	142,591	8.3	7.0-10.0
IUD Type unknown	21	32,402	6.5	4.2-9.9
Depomedroxyprogesterone acetate	19	88,097	2.2	1.4-3.4
Progesting-only oral contraceptive	114	69,502	16.4	13.7-19.7
Implant	26	107,795	2.4	1.6-3.5
Non-use with prior use in the last 12months	1,356	509,254	26.6	25.2-28.1
Non-use with no prior use in the last 12months	3,425	3,441,046	10.0	9.6-10.3
Overall[1]	**5,711**	**5,789,224**	**9.9**	**9.6-10.1**

15.5.6 Table xx. Ectopic Pregnancy Incidence by Prescription Contraceptive Method 2010-2019 (KPSC) - N=1,684,201

Method	Number of Ectopic Pregnancies	Woman-years	Incidence per 10,000 woman years	95% Confidence Interval
Combined Hormonal Contraceptive	484	890,954	5.4	5.0-5.9
Levonorgestrel IUD	126	301,782	4.2	3.5-5.0
Copper IUD	76	101,327	7.5	6.0-9.4
IUD Type unknown	41	41,182	10.0	7.3-13.5
Depomedroxyprogesterone acetate	14	72,391	1.9	1.1-3.2
Progesting-only oral contraceptive	90	48,816	18.4	15.0-22.7
Implant	13	80,049	1.6	0.9-2.8
Non-use with prior use in the last 12months	1,105	546,439	20.2	19.1-21.4
Non-use with no prior use in the last 12months	3,776	4,037,678	9.4	9.1-9.7
Overall[1]	**5,725**	**6,120,618**	**9.2**	**9.1-9.4**

15.5.7 Appendix Table xxi. Accuracy (PPV) of electronic algorithm compared to chart review by contraceptive method - KPNC

	Total N=361					
	Number of periods reviewed	Mean Number of days used [SD] Median (IQR)	Number use confirmed	Number uncertain	PPV (confirmed/ reviewed)	(95% CI)
Overall	361	485.9 (584.9) 236 (106-671)	340	6	94.2%	(91.3-96.4)
By Method						
Copper IUD	26	522.8 (481.6) 435 (72-1086)	26	0	100.0%	(86.8-100.0)
Levonorgestrel IUD	63	627.4 (554.3) 489 (205-1016)	62	0	98.4%	(91.5-10.00)
IUD type unknown	13	705.2 (487.6) 734 (297-953)	12	0	92.3%	(64.0-99.8)
Combined OCP	82	372.1 (554.7) 166 (106-441)	76	3	92.7%	(84.8-97.3)
Progesterone-only OCP	37	149.5 (93.2) 106 (106-176)	32	3	86.5%	(71.2-95.5)
Depot medroxyprogesterone acetate	22	158.9 (125.1) 105 (91-255)	21	0	95.5%	(77.2-99.9)
Transdermal Patch or Vaginal Ring	32	343.8 (456.8) 211 (106-377)	29	0	90.6%	(75.0-98.0)
Implant	36	411.3 (379.3) 254 (114-750)	33	0	91.7%	(77.5-98.3)
No prescription method used	50	955.2 (868.9) 776 (273-1397)	49	0	98.0%	(89.4-100.0)

15.5.8 Appendix Table xxii. Accuracy (PPV) of electronic algorithm compared to chart review by contraceptive method - KPSC

	Total N=348					
	Number of periods reviewed	Mean Number of days used [SD] Median (IQR)	Number use confirmed	Number uncertain	PPV (confirmed/ reviewed)	(95% CI)
Overall	348	445.6 (554.2) 216 (106-550)	319	5	91.7%	(88.3-94.4)
By Method						
Copper IUD	29	396.6 (325.6) 293 (137-561)	29	0	100.0%	(88.1-100.0)
Levonorgestrel IUD	53	508.1 (514.3) 329 (143-871)	50	0	94.3%	(84.3-98.8)
IUD type unknown	13	607.5 (750.2) 292 (62-793)	11	0	84.6%	(54.5-98.1)
Combined OCP	78	241.8 (246.6) 135 (106-321)	71	3	91.0%	(82.4-96.3)
Progesterone-only OCP	34	158.4 (110.8) 106 (106-187)	30	1	88.2%	(72.6-96.7)
Depot medroxyprogesterone acetate	24	148.2 (108.9) 100 (91-171)	24	0	100.0%	(85.8-100.0)
Transdermal Patch or Vaginal Ring	25	217.7 (238.5) 106 (97-287)	23	1	92.0%	(74.0-99.0)
Implant	38	564.3 (362.6) 525 (197-870)	29	0	76.3%	(59.8-88.6)
No prescription method used	54	1001.2 (913.4) 700 (275-1492)	52	0	96.3%	(87.3-99.6)

15.5.9 Appendix Table xxiii. Distribution of cohort characteristics based on earliest contraceptive method use status during the study period - KPNC

Characteristics	Total N=1,519,907	Any Contraceptive[a] N=347,145	Non-Use	
			Discontinued ≤ 1 year[b] N= 105,759	Discontinued > 1 year[c] N=1,067,003
Age, Mean (SD)	27.7 (9.1)	28.8 (7.2)	29.0 (7.1)	27.2 (9.7)
Age, year (%)				
15-19	387,845 (25.5)	38,019 (10.9)	11,042 (10.4)	338,784 (31.7)
20-29	469,170 (30.9)	158,320 (45.6)	46,290 (43.8)	264,560 (24.8)
30-34	257,219 (16.9)	72,400 (20.9)	23,707 (22.4)	161,112 (15.1)
35-44	405,673 (26.7)	78,406 (22.6)	24,720 (23.4)	302,547 (28.4)
Race/Ethnicity (%)				
Non-Hispanic White	574,219 (37.8)	169,649 (48.9)	44,930 (42.5)	359,640 (33.7)
Non-Hispanic Black	112,408 (7.4)	22,750 (6.6)	9,620 (9.1)	80,038 (7.5)
Hispanic	358,705 (23.6)	7,6474 (22)	25,842 (24.4)	256,389 (24)
Asian/Pacific Islander	337,248 (22.2)	59,468 (17.1)	19,543 (18.5)	258,237 (24.2)
Other/Unknown	137,327 (9.0)	18,804 (5.4)	5,824 (5.5)	112,699 (10.6)
Smoking Status (%)				
Never	1,158,170 (76.2)	269,574 (77.7)	78,504 (74.2)	810,092 (75.9)
Former	112,061 (7.4)	32,701 (9.4)	10,716 (10.1)	68,644 (6.4)
Current	163,152 (10.7)	42,590 (12.3)	15,357 (14.5)	105,205 (9.9)
Unknown	86,524 (5.7)	2,280 (0.7)	1,182 (1.1)	83,062 (7.8)
Parity (%)				
Nullipara	309,310 (20.4)	124,488 (35.9)	37,553 (35.5)	147,269 (13.8)
Multipara	416,003 (27.4)	124,088 (35.7)	42,157 (39.9)	249,758 (23.4)
Unknown	794,594 (52.3)	98,569 (28.4)	26,049 (24.6)	669,976 (62.8)
Household income[d], USD (%)				
< 30,000	65,156 (4.3)	13,390 (3.9)	4,617 (4.4)	47,149 (4.4)
30,000-49,999	279,916 (18.4)	61,422 (17.7)	19,758 (18.7)	198,736 (18.6)
50,000-69,999	382,097 (25.1)	89,073 (25.7)	27,211 (25.7)	265,813 (24.9)
70,000-89,999	339,670 (22.3)	78,963 (22.7)	23,834 (22.5)	236,873 (22.2)
≥ 90,000	450,785 (29.7)	104,084 (30)	30,284 (28.6)	316,417 (29.7)
Unknown	2,283 (0.2)	213 (0.1)	55 (0.1)	2,015 (0.2)

Abbreviations: KPNC, Kaiser Permanente Northern California; SD; Standard Deviation; USD, United States Dollar. [a]Combined Oral Contraceptive/Patch/Ring, Progestin-only Oral Contraceptive Pills, Implants, Depomedroxyprogesterone acetate, Intrauterine Device; [b]Patient stopped using contraceptive within 1 year prior to first method start; [c]Patient stopped using contraceptive >1 year prior to first method start; [d]Median family household income based on census tract of residence; All differences in proportion are statistically significant ($P < .001$)

15.5.10 Appendix Table xxiv. Distribution of cohort characteristics based on earliest contraceptive method use status during the study period - KPSC

Characteristics	Total N=1,684,191	Any Contraceptive[a] N=312,634	Non-Use	
			Discontinued ≤ 1 year[b] N= 119,371	Discontinued > 1 year[c] N=1,252,186
Age, Mean (SD)	27.7 (8.8)	28.3 (7.1)	28.1 (7.2)	27.6 (9.3)
Age, year (%)				
15-19	426,275 (25.3)	37,332 (11.9)	15,728 (13.2)	373,215 (29.8)
20-29	544,049 (32.3)	149,137 (47.7)	54,821 (45.9)	340,091 (27.2)
30-34	270,254 (16.0)	62,278 (19.9)	24,373 (20.4)	183,603 (14.7)
35-44	443,613 (26.3)	63,887 (20.4)	24,449 (20.5)	355,277 (28.4)
Race/Ethnicity (%)				
Non-Hispanic White	457,033 (27.1)	117,172 (37.5)	36,683 (30.7)	303,178 (24.2)
Non-Hispanic Black	131,435 (7.8)	21,380 (6.8)	10,998 (9.2)	99,057 (7.9)
Hispanic	744,665 (44.2)	123,219 (39.4)	53,405 (44.7)	568,041 (45.4)
Asian/Pacific Islander	190,990 (11.3)	30,161 (9.6)	10,971 (9.2)	149,858 (12.0)
Other/Unknown	160,068 (9.5)	20,702 (6.6)	7,314 (6.1)	132,052 (10.5)
Smoking Status (%)				
Never	1,096,481 (65.1)	237,327 (75.9)	88,571 (74.2)	770,583 (61.5)
Former	86,992 (5.2)	21,948 (7.0)	8,966 (7.5)	56,078 (4.5)
Current	97,708 (5.8)	21,341 (6.8)	9,836 (8.2)	66,531 (5.3)
Unknown	403,010 (23.9)	32,018 (10.2)	11,998 (10.1)	358,994 (28.7)
Parity (%)				
Nullipara	249,479 (14.8)	82,589 (26.4)	31,083 (26.0)	135,807 (10.8)
Multipara	444,366 (26.4)	105,583 (33.8)	44,419 (37.2)	294,364 (23.5)
Unknown	990,346 (58.8)	124,462 (39.8)	43,869 (36.8)	822,015 (65.6)
Household income[d], USD (%)				
< 30,000	73,267 (4.4)	11,112 (3.6)	5,341 (4.5)	56,814 (4.5)
30,000-49,999	418,354 (24.8)	68,350 (21.9)	29,750 (24.9)	320,254 (25.6)
50,000-69,999	474,558 (28.2)	86,424 (27.6)	33,699 (28.2)	354,435 (28.3)
70,000-89,999	352,160 (20.9)	70,057 (22.4)	25,034 (21.0)	257,069 (20.5)
≥ 90,000	361,283 (21.5)	75,679 (24.2)	25,161 (21.1)	260,443 (20.8)
Unknown	4,569 (0.3)	1,012 (0.3)	386 (0.3)	3,171 (0.3)

Abbreviations: KPSC, Kaiser Permanente Southern California; SD; Standard Deviation; USD, United States Dollar. [a]Combined Oral Contraceptive/Patch/Ring, Progestin-only Oral Contraceptive Pills, Implants, Depomedroxyprogesterone acetate, Intrauterine Device; [b]Patient stopped using contraceptive within 1 year prior to first method start; [c]Patient stopped using contraceptive >1 year prior to first method start; [d]Median family household income based on census tract of residence; All differences in proportion are statistically significant ($P < .001$)

15.5.11 Appendix Table xxv. Incidence rates and hazard ratios expressing the association of demographic characteristics with ectopic pregnancy risk - KPNC

Characteristics	Person-Year N=5,783,917	EP N=5,582	Rate[a] 9.65	Hazard Ratio (95% CI) Crude	Hazard Ratio (95% CI) Adjusted[b]
Age, year					
15-19	1,027,263	139	1.35	0.12 (0.10, 0.15)	0.16 (0.13, 0.19)
20-29	1,715,372	1,785	10.41	1.00 (reference)	1.00 (reference)
30-34	982,287	1,868	19.02	1.81 (1.69, 1.93)	1.42 (1.32, 1.52)
35-44	2,058,995	1,790	8.69	0.84 (0.79, 0.90)	0.64 (0.59, 0.69)
Race/Ethnicity					
Non-Hispanic White	2,279,237	1,951	8.56	1.00 (reference)	1.00 (reference)
Non-Hispanic Black	453,665	712	15.69	1.84 (1.69, 2.00)	1.63 (1.49, 1.78)
Hispanic	1,396,745	1,474	10.55	1.26 (1.15, 1.32)	1.24 (1.16, 1.33)
Asian/Pacific Islander	1,333,617	1,308	9.81	1.15 (1.07, 1.23)	1.04 (0.97, 1.12)
Other/Unknown	320,653	137	4.27	0.50 (0.42, 0.59)	0.65 (0.55, 0.78)
Household income[c], USD					
< 30,000	215,437	247	11.47	1.31 (1.14, 1.49)	1.12 (0.97, 1.28)
30,000-49,999	996,433	1,076	10.80	1.23 (1.14, 1.33)	1.10 (1.02, 1.19)
50,000-69,999	1,443,528	1,400	9.70	1.11 (1.03, 1.19)	1.03 (0.96, 1.11)
70,000-89,999	1,325,872	1,277	9.63	1.10 (1.02, 1.18)	1.05 (0.97, 1.13)
≥ 90,000	1,796,301	1,578	8.78	1.00 (reference)	1.00 (reference)
Unknown	6,347	4	6.30	0.72 (0.27, 1.91)	1.08 (0.40, 2.88)
Parity					
Nullipara	1,564,774	1,812	11.58	1.00 (reference)	1.00 (reference)
Multipara	2,306,197	2,923	12.67	1.10 (1.04, 1.17)	1.19 (1.11, 1.27)
Unknown	1,912,947	847	4.43	0.36 (0.33, 0.39)	0.69 (0.64, 0.76)
Smoking Status					
Never	4,525,641	3,999	8.84	1.00 (reference)	1.00 (reference)
Former	440,302	580	13.17	1.49 (1.37, 1.63)	1.27 (1.16, 1.38)
Current	684,032	987	14.43	1.64 (1.53, 1.75)	1.47 (1.37, 1.58)
Unknown	133,942	16	1.19	0.13 (0.08, 0.22)	0.27 (0.16, 0.45)

Abbreviations: KPNC, Kaiser Permanente Northern California; EP, ectopic pregnancy; CI, confidence interval; USD, United States Dollar
[a]Incidence rate is shown per 10,000 person-years; [b]Hazard ratios were adjusted for covariates listed in Tables 2 and 3; [c]Median family household income based on census tract of residence

15.5.12 Appendix Table xxvi. Incidence rates and hazard ratios expressing the association of demographic characteristics with ectopic pregnancy risk - KPSC

Characteristics	Person-Year N=6,120,612	EP N=5,722	Rate[a] 9.35	Hazard Ratio (95% CI) Crude	Hazard Ratio (95% CI) Adjusted[b]
Age, year					
15-19	978,046	167	1.71	0.16 (0.14, 0.19)	0.20 (0.17,0.23)
20-29	1,997,758	2,008	10.05	1.00 (reference)	1.00 (reference)
30-34	1,016,942	1,828	17.98	1.78 (1.67, 1.90)	1.38 (1.29, 1.48)
35-44	2,127,866	1,719	8.08	0.81 (0.76, 0.86)	0.61 (0.57, 0.66)
Race/Ethnicity					
Non-Hispanic White	1,652,304	1,318	7.98	1.00 (reference)	1.00 (reference)
Non-Hispanic Black	540,112	777	14.39	1.80 (1.65, 1.97)	1.65 (1.51, 1.81)
Hispanic	2,889,879	2,901	10.04	1.26 (1.18, 1.34)	1.23 (1.15, 1.32)
Asian/Pacific Islander	706,012	616	8.73	1.09 (0.99, 1.20)	1.01 (0.92, 1.11)
Other/Unknown	332,305	110	3.31	0.41 (0.34, 0.50)	0.51 (0.42, 0.63)
Household income[c], USD					
< 30,000	283,366	332	11.72	1.48 (1.31, 1.68)	1.18 (1.04, 1.34)
30,000-49,999	1,536,694	1,575	10.25	1.29 (1.20, 1.40)	1.08 (0.99, 1.17)
50,000-69,999	1,763,487	1,670	9.47	1.20 (1.11, 1.29)	1.05 (0.97, 1.14)
70,000-89,999	1,282,554	1,152	8.98	1.13 (1.04, 1.23)	1.04 (0.96, 1.14)
≥ 90,000	1,246,075	985	7.90	1.00 (reference)	1.00 (reference)
Unknown	8,437	8	9.48	1.21 (0.60, 2.43)	1.25 (0.62, 2.50)
Parity					
Nullipara	1,273,897	1,516	11.90	1.00 (reference)	1.00 (reference)
Multipara	2,399,848	2,946	12.28	1.04 (0.98, 1.11)	1.14 (1.07, 1.23)
Unknown	2,446,868	1,260	5.15	0.41 (0.38, 0.45)	0.69 (0.63, 0.74)
Smoking Status					
Never	4,090,640	4,077	9.97	1.00 (reference)	1.00 (reference)
Former	431,563	563	13.05	1.31 (1.20, 1.43)	1.12 (1.03, 1.23)
Current	292,354	435	14.88	1.48 (1.34, 1.64)	1.36 (1.23, 1.51)
Unknown	1,306,055	647	4.95	0.50 (0.45, 0.54)	0.66 (0.60, 0.71)

Abbreviations: KPSC, Kaiser Permanente Southern California; EP, ectopic pregnancy; CI, confidence interval; USD, United States Dollar
[a]Incidence rate is shown per 10,000 person-years; [b]Hazard ratios were adjusted for covariates listed in Tables 2 and 3; [c]Median family household income based on census tract of residence

15.5.13 Appendix Table xxvii. Incidence rates and hazard ratios expressing the association of potential medical- and obstetrical-related risk factors with ectopic pregnancy risk - KPNC

History of potential risk factors	Total Person-Year	EP (N)	Incidence Rate[a]	Hazard Ratio (95% CIs)	
				Crude	Adjusted[b]
Ectopic Pregnancy					
No	5,781,675	5,565	9.63	1.00 (ref.)	1.00 (ref.)
Yes	2,242	17	75.81	7.94 (4.93, 12.78)	2.36 (1.45, 3.84)
Sexually Transmitted Disease					
No	5,599,207	5,159	9.21	1.00 (ref.)	1.00 (ref.)
Yes	184,710	423	22.90	2.52 (2.28, 2.79)	1.93 (1.74, 2.15)
Pelvic Inflammatory Disease					
No	5,768,555	5,515	9.56	1.00 (ref.)	1.00 (ref.)
Yes	15,362	67	43.61	4.59 (3.61, 5.84)	1.66 (1.30, 2.13)
Infertility					
No	5,573,278	4,494	8.06	1.00 (ref.)	1.00 (ref.)
Yes	210,639	1088	51.65	6.71 (6.27, 7.18)	4.73 (4.40, 5.09)
Endometriosis					
No	5,533,891	5,081	9.18	1.00 (ref.)	1.00 (ref.)
Yes	250,027	501	20.04	2.21 (2.02, 2.43)	1.35 (1.22, 1.48)
Congenital Malformation					
No	5,766,517	5,523	9.58	1.00 (ref.)	1.00 (ref.)
Yes	17,401	59	33.91	3.56 (2.75, 4.60)	1.34 (1.03, 1.74)
Pelvic Organ Surgeries					
Cesarean Section					
No	5,255,691	4,906	9.33	1.00 (ref.)	1.00 (ref.)
Yes	528,226	676	12.80	1.38 (1.27, 1.50)	0.92 (0.84, 1.00)
Tubal ligation/occlusion					
No	5,694,725	5,538	9.72	1.00 (ref.)	1.00 (ref.)
Yes	89,192	44	4.93	0.51 (0.38, 0.68)	0.35 (0.26, 0.47)
Myomectomy					
No	5,761,127	5,512	9.57	1.00 (ref.)	1.00 (ref.)
Yes	22,790	70	30.71	3.23 (2.55, 4.09)	1.01 (0.79, 1.29)
Adnexal surgery					
No	5,719,902	5,349	9.35	1.00 (ref.)	1.00 (ref.)
Yes	64,015	233	36.40	3.95 (3.46, 4.51)	1.61 (1.39, 1.86)
Appendectomy					
No	5,731,486	5,527	9.64	1.00 (ref.)	1.00 (ref.)
Yes	52,431	55	10.49	1.09 (0.84, 1.42)	1.01 (0.78, 1.32)
Any pelvic surgery					
No	5,113,140	4,602	9.00	1.00 (ref.)	1.00 (ref.)
Yes	670,777	980	14.61	1.63 (1.52, 1.74)	0.99 (0.92, 1.07)

Abbreviations: KPNC, Kaiser Permanente Northern California; EP, ectopic pregnancy; CI, confidence interval. [a]Incidence rate is shown per 10,000 person-years; [b]Hazard ratios were adjusted for factors listed in Tables 2 and 3; [c]Patient stopped using contraceptive >1 year prior to each method start; [d]Patient stopped using contraceptive within 1 year prior to each method start

15.5.14 Appendix Table xxviii. Incidence rates and hazard ratios expressing the association of potential medical- and obstetrical-related risk factors with ectopic pregnancy risk - KPSC

History of potential risk factors	Total Person-Year	EP (N)	Incidence Rate[a]	Hazard Ratio (95% CIs)	
				Crude	Adjusted[b]
Ectopic Pregnancy					
No	6,119,599	5,705	9.32	1.00 (ref.)	1.00 (ref.)
Yes	1,013	17	167.81	17.59 (10.91, 28.33)	4.46 (2.74, 7.25)
Sexually Transmitted Disease					
No	5,878,292	5,266	8.96	1.00 (ref.)	1.00 (ref.)
Yes	242,320	456	18.82	2.09 (1.90, 2.31)	1.69 (1.53, 1.87)
Pelvic Inflammatory Disease					
No	6,106,923	5,684	9.31	1.00 (ref.)	1.00 (ref.)
Yes	13,689	38	27.76	2.95 (2.14, 4.06)	1.17 (0.85, 1.62)
Infertility					
No	5,916,595	4,739	8.01	1.00 (ref.)	1.00 (ref.)
Yes	204,016	983	48.18	6.20 (5.78, 6.65)	4.41 (4.09, 4.75)
Endometriosis					
No	5,933,213	5,388	9.08	1.00 (ref.)	1.00 (ref.)
Yes	187,399	334	17.82	1.95 (1.74, 2.18)	1.09 (0.97, 1.23)
Congenital Malformation					
No	6,104,184	5,669	9.29	1.00 (ref.)	1.00 (ref.)
Yes	16,428	53	32.26	3.44 (2.62, 4.51)	1.61 (1.22, 2.11)
Pelvic Organ Surgeries					
Cesarean Section					
No	5,484,338	4,917	8.97	1.00 (ref.)	1.00 (ref.)
Yes	636,274	805	12.65	1.41 (1.31, 1.52)	1.00 (0.92, 1.09)
Tubal ligation/occlusion					
No	5,981,621	5,658	9.46	1.00 (ref.)	1.00 (ref.)
Yes	138,991	64	4.60	0.48 (0.37, 0.61)	0.33 (0.26, 0.43)
Myomectomy					
No	6,094,971	5,673	9.31	1.00 (ref.)	1.00 (ref.)
Yes	25,641	49	19.11	2.03 (1.53, 2.69)	0.74 (0.56, 0.99)
Adnexal surgery					
No	6,046,301	5,433	8.99	1.00 (ref.)	1.00 (ref.)
Yes	74,311	289	38.89	4.32 (3.83, 4.87)	2.31 (2.02, 2.63)
Appendectomy					
No	6,067,906	5,667	9.34	1.00 (ref.)	1.00 (ref.)
Yes	52,706	55	10.44	1.11 (0.85, 1.44)	1.00 (0.77, 1.31)
Any pelvic surgery					
No	5,312,976	4,590	8.64	1.00 (ref.)	1.00 (ref.)
Yes	807,635	1,132	14.02	1.63 (1.52, 1.74)	1.07 (0.99, 1.15)

Abbreviations: KPSC, Kaiser Permanente Southern California; EP, ectopic pregnancy; CI, confidence interval. [a]Incidence rate is shown per 10,000 person-years; [b]Hazard ratios were adjusted for factors listed in Tables 2 and 3; [c]Patient stopped using contraceptive >1 year prior to each method start; [d]Patient stopped using contraceptive within 1 year prior to each method start

15.5.15 Appendix Table xxix. Incidence rates and hazard ratios expressing the association between contraceptive methods and ectopic pregnancy risk - KPNC

Contraceptive Method	Total Person-Year	EP (N)	Incidence Rate[a]	Hazard Ratio (95% CIs)	
				Crude	Adjusted[b]
Non-Use (discontinued > 1 year)[c]	3,436,654	3,304	9.61	1.00 (Ref.)	1.00 (Ref.)
Non-Use (discontinued ≤ 1 year)[d]	508,717	1,354	26.62	2.79 (2.62, 2.97)	1.99 (1.87, 2.13)
DMPA	88,084	19	2.16	0.23 (0.14, 0.35)	0.18 (0.11, 0.28)
CHC use	920,250	451	4.90	0.51 (0.46, 0.56)	0.47 (0.43, 0.52)
Progestin-only OCP use	69,489	114	16.41	1.71 (1.42, 2.07)	1.13 (0.93, 1.36)
Implant	107,772	26	2.41	0.25 (0.17, 0.37)	0.22 (0.15, 0.33)
Intrauterine Device (IUD)	652,953	314	4.81	0.50 (0.44, 0.56)	0.39 (0.34, 0.43)
Levonorgestrel IUD	478,040	177	3.70	0.38 (0.33, 0.45)	0.29 (0.25, 0.34)
Copper-containing IUD	142,524	116	8.14	0.85 (0.70, 1.02)	0.67 (0.55, 0.80)
Unknown IUD type	32,388	21	6.48	0.68 (0.44, 1.04)	0.55 (0.36, 0.85)

Abbreviations: KPNC, Kaiser Permanente Northern California; EP, ectopic pregnancy; CI, confidence interval; DMPA, Depomedroxyprogesterone acetate; CHC, Combined Hormonal Contraceptives (including oral contraceptive, transdermal patch and vaginal ring); OCP, Oral Contraceptive Pills; [a]Incidence rate is shown per 10,000 person-years; [b]Hazard ratios were adjusted for factors listed in Tables 2 and 3; [c]Patient stopped using contraceptive >1 year prior to each method start; [d]Patient stopped using contraceptive within 1 year prior to each method start

15.5.16 Appendix Table xxx. Incidence rates and hazard ratios expressing the association between contraceptive methods and ectopic pregnancy risk - KPSC

Contraceptive Method	Total Person-Year	EP (N)	Incidence Rate[a]	Hazard Ratio (95% CIs)	
				Crude	Adjusted[b]
Non-Use (discontinued > 1 year)[c]	4,037,676	3,775	9.35	1.00 (Ref.)	1.00 (Ref.)
Non-Use (discontinued ≤ 1 year)[d]	546,420	1,104	20.20	2.17 (2.03, 2.32)	1.54 (1.43, 1.65)
DMPA	72,391	14	1.93	0.21 (0.12, 0.35)	0.15 (0.09, 0.26)
CHC use	890,964	483	5.42	0.58 (0.53, 0.64)	0.51 (0.46, 0.56)
Progestin-only OCP use	48,816	90	18.44	1.97 (1.60, 2.43)	1.16 (0.94, 1.43)
Implant	80,050	13	1.62	0.17 (0.10, 0.30)	0.14 (0.08, 0.23)
Intrauterine Device (IUD)	444,295	243	5.47	0.58 (0.51, 0.66)	0.43 (0.37, 0.49)
Levonorgestrel IUD	301,769	126	4.18	0.44 (0.37, 0.53)	0.32 (0.27, 0.38)
Copper-containing IUD	101,324	76	7.50	0.79 (0.63, 1.00)	0.60 (0.47, 0.75)
Unknown IUD type	41,201	41	9.95	1.07 (0.79, 1.46)	0.87 (0.64, 1.18)

Abbreviations: KPSC, Kaiser Permanente Southern California; EP, ectopic pregnancy; CI, confidence interval; DMPA, Depomedroxyprogesterone acetate; CHC, Combined Hormonal Contraceptives (including oral contraceptive, transdermal patch and vaginal ring); OCP, Oral Contraceptive Pills; [a]Incidence rate is shown per 10,000 person-years; [b]Hazard ratios were adjusted for factors listed in Tables 2 and 3; [c]Patient stopped using contraceptive >1 year prior to each method start; [d]Patient stopped using contraceptive within 1 year prior to each method start

Annex 5: Signature pages

Signature Page - OS Epidemiologist

Title	Incidence and Trend of Ectopic Pregnancy 2009-2018 - A population-based Study (EPR Study)
Protocol version and date	V1.0, 15/11/2021
IMPACT study number	20257
Study type / Study phase	Observational, Phase IV <PASS> PASS: ☐ YES ☒ NO
Active substance	Levonorgestrel
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 12/8/2021,

PPD

Signature Page – Global Safety Lead

Title	Incidence and Trend of Ectopic Pregnancy 2009-2018 - A population-based Study (EPR Study)
Protocol version and date	V1.0, 15/11/2021
IMPACT study number	20257
Study type / Study phase	Observational, Phase IV <PASS> PASS: ☐ YES ☒ NO
Active substance	Levonorgestrel
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 12/7/2021 _____,

_____ PPD _____

Signature Page - OS Medical Expert

Title	Incidence and Trend of Ectopic Pregnancy 2009-2018 - A population-based Study (EPR Study)
Protocol version and date	V1.0, 15/11/2021
IMPACT study number	20257
Study type / Study phase	Observational, Phase IV <PASS> PASS: ☐ YES ☒ NO
Active substance	Levonorgestrel
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 12/8/2021 _____,

_____ PPD _____

Signature Page – Principal Investigator (external)

Title	Incidence and Trend of Ectopic Pregnancy 2009-2018 - A population-based Study (EPR Study)
Protocol version and date	V1.0, 15/11/2021
IMPACT study number	20257
Study type / Study phase	Observational, Phase IV <PASS> PASS: ☐ YES ☒ NO
Active substance	Levonorgestrel
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature: 12/14/2021,

PPD