



## Clinical Study Synopsis

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## 1. Abstract

<b>Acronym/Title</b>	<b>Incidence and Trend of Ectopic Pregnancy 2009-2018 - A population-based Study (EPR Study)</b>
<b>Study type / Study phase</b>	Observational, Phase IV
<b>IMPACT study number</b>	20257
<b>Medicinal product / Active substance / Medical Device / Combination Product</b>	Hormonal (Levonorgestrel-releasing intrauterine systems) and non-hormonal intrauterine devices
<b>Comparator / Reference therapy</b>	Oral contraception, Depot medroxyprogesterone Acetate, Transdermal Patch, Vaginal Ring, Subdermal Implant
<b>Study Initiator and Funder</b>	Bayer AG, 13342 Berlin
<b>Report version and date</b> <b>Author</b>	V 1.0 15 November 2021 PPD Kaiser Permanente Northern California
<b>Keywords</b>	Ectopic pregnancy, Intrauterine Device, hormonal Contraception, risk factors
<b>Rationale and background</b>	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.
<b>Research question and objectives</b>	The study was designed to address the following research questions:



	<ul style="list-style-type: none"> <li>• 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?</li> <li>• What are the temporal trends in ectopic pregnancy incidence rates over the last decade overall and in women with current contraceptive use?</li> <li>• What are the potential risk factors associated with ectopic pregnancy in women with current IUD, OCP, and DMPA use?</li> <li>• What are the trends in management of ectopic pregnancy over the last decade?</li> </ul> <p>We also conducted a study to validate ectopic pregnancy case ascertainment for the current study using administrative, claims, and electronic health records.</p>
<b>Study design</b>	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.
<b>Setting</b>	The study was conducted at KPNC and KPSC, which represent the two largest of KP's nine regional integrated health care systems nationwide.
<b>Subjects and study size, including dropouts</b>	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.
<b>Variables and data sources</b>	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.
<b>Results</b>	<p>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; <math>p &lt; 0.0001</math>) and infertility (adjusted HR 4.79, 95% CI 3.98, 5.77; <math>p &lt; 0.001</math>).</p>
<b>Conclusion</b>	<p>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.</p>