Science For A Better Life

Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Abstract

Title

Study on the Association of Uterine Perforation and IUD Expulsion With Breastfeeding Status at the Time of IUD Insertion and Postpartum Timing of IUD Insertion in Electronic Medical Record Databases – A Postmarketing Requirement for Mirena (APEX IUD)

Keywords

Intrauterine device, postpartum, breastfeeding, menorrhagia, cohort study, IUD expulsion, uterine perforation

Rationale and background

Mirena, a levonorgestrel (LNG)-releasing intrauterine system (LNG-IUD), was approved by the United States (US) Food and Drug Administration (FDA) for use in the US in December 2000. In August 2015, FDA communicated to Bayer a new postmarketing requirement to conduct a study of incidence and risk factors for uterine perforation related to breastfeeding and timing of postpartum intrauterine device (IUD) insertion in US women. The concerns described by the FDA related to results from the European Active Surveillance Study for Intrauterine Devices (EURAS-IUD), which found an increased risk of uterine perforation with breastfeeding at the time of IUD insertion and with IUD insertions within 36 weeks of delivery in the studied European population.

Research question and objectives

The overall goal of this study was to assess the impact of breastfeeding and timing of postpartum IUD insertion on uterine perforation and IUD expulsion (evaluated separately) in a representative population of US women. The study also evaluated risk of these outcomes in women with a recent diagnosis of menorrhagia (i.e., within the 12 months before the IUD insertion) versus no recent diagnosis and by IUD type (copper versus LNG- releasing). Incidence rates and cumulative incidence of these events among the different exposure groups were calculated. An assessment of statistical interaction between postpartum timing of IUD insertion and breastfeeding at the time of IUD insertion for uterine perforation was done. Other statistical interactions were evaluated for IUD type with breastfeeding at the time of IUD insertion or postpartum timing of IUD insertion for both uterine perforation and IUD expulsion.

Study design

The study was a retrospective cohort study set within four health care system data sources with electronic health records.

Setting

This study was conducted using data from three health care systems with electronic health records (Kaiser Permanente Northern California [KPNC], Kaiser Permanente Southern California [KPSC], Kaiser Permanente Washington [KPWA]) and one research institute with access to a health

information exchange, Regenstrief Institute (RI). The investigators at these sites (research partners) worked collaboratively to develop a common approach to study design and implementation.

Subjects and study size, including dropouts

The study included 326,658 women with at least one IUD insertion identified during the study period. The number of women included from each site differed (KPNC, 161,442; KPSC, 123,214; KPWA, 20,526; and RI, 21,476).

Variables and data sources

Variables included baseline characteristics such as demographic characteristics, clinical characteristics, procedure-related characteristics, indicators of a difficult IUD insertion, year of IUD insertion, data source, and provider-related characteristics. The exposures included postpartum timing of IUD insertion (using different time categories), breastfeeding status (yes or no) at the time of IUD insertion, type of IUD inserted (copper vs. LNG-releasing), and recent diagnosis of menorrhagia. The outcomes were uterine perforation and IUD expulsion. Continuous enrollment time was also measured. This information came from medical records that included both structured data (e.g., ICD [*International Classification of Diseases*] diagnosis and procedure codes, medication codes, and Common Procedural Terminology codes) and unstructured data (e.g., clinical notes).

Results

The crude incidence of uterine perforation ranged from 2.2 to 5.5 per 1,000 person-years for different categories of time of postpartum IUD placement among women who were ≤ 52 weeks postpartum and was 0.68 per 1,000 person-years for women who were > 52 weeks postpartum or had no recorded delivery in the last year. The risk (based on adjusted hazard ratios) of uterine perforation was approximately 190% to 570% higher among women with earlier postpartum IUD insertions (4 days to ≤ 6 weeks, 6 to ≤ 14 weeks, 14 to ≤ 52 weeks) than among those with IUD insertions > 52 weeks postpartum or with no recorded delivery in the previous 12 months (main comparator group). Among women with an IUD insertion within 3 days of delivery, the risk of uterine perforation was 170% higher than for women with insertions > 52 weeks postpartum or with no recorded delivery in the previous 12 months. The crude incidence of uterine perforation in women who were breastfeeding at the time of IUD insertion and within 52 weeks postpartum was 4.2 per 1,000 person-years and was 2.5 per 1,000 person-years for women who were not breastfeeding and within 52 weeks postpartum at the time of IUD insertion. Women who were breastfeeding at the time of IUD insertion and within 52 weeks postpartum were at a 40% higher risk of uterine perforation than women who were not breastfeeding and within 52 weeks postpartum.

The crude incidence of IUD expulsion ranged from 9.3 to 46.5 per 1,000 person-years in different categories of time of postpartum IUD placement among women who were ≤ 52 weeks postpartum and was 14.9 per 1,000 person-years for women who were > 52 weeks postpartum or had no recorded delivery in the last year. The risk of IUD expulsion (based on adjusted hazard ratios) was 20% higher in women with IUD insertions 4 days to 6 weeks postpartum and 40% higher in women with IUD insertions 14 to ≤ 52 weeks postpartum than in women with IUD insertions more than 52 weeks postpartum or with no recorded delivery. Among women with an IUD insertion within 3 days of delivery, risk of IUD expulsion was 430% higher than in those with an IUD insertion > 52 weeks postpartum or with no recorded delivery. The crude incidence of IUD expulsion was

10.2 per 1,000 person-years in women who were breastfeeding and within 52 weeks postpartum at the time of IUD insertion and 14.6 per 1,000 person-years for women who were not breastfeeding and were within 52 weeks postpartum at the time of IUD insertion. Women who were breastfeeding at the time of IUD insertion and within 52 weeks postpartum had a 30% lower risk of IUD expulsion than those who were not breastfeeding and were within 52 weeks postpartum at IUD insertion.

The crude incidence rates of uterine perforation were 1.6 per 1,000 person-years for women with LNG-IUDs and 1.3 per 1,000 person-years for women with copper IUDs. For IUD expulsion, the crude incidence rates were 14.0 per 1,000 person-years for women with LNG-IUDs and 14.1 per 1,000 person-years for women with copper IUDs. Women with LNG-IUDs were at a 50% higher risk of uterine perforation and 30% lower risk of IUD expulsion than women with copper IUDs.

Among women without a recorded delivery in the previous 52 weeks, the crude incidence rates of uterine perforation were 1.0 per 1,000 person-years in women with a recent diagnosis of menorrhagia (i.e., in the previous 12 months) and 0.6 per 1,000 person-years in those without a recent diagnosis. For IUD expulsion, the crude incidence rates were 40.0 per 1,000 person-years in women with a recent diagnosis of menorrhagia and 10.9 per 1,000 person-years in women without a recent diagnosis in the population of women without a recorded delivery in the previous 52 weeks. In this same population, the risk of uterine perforation was 50% higher and risk of IUD expulsion was about 180% higher in women with a diagnosis of menorrhagia in the previous 12 months than in women without such a diagnosis.

Discussion

Overall incidence of IUD-associated uterine perforation was low (ranging from 0.6 to 5.5 per 1,000 person-years depending on the exposure [e.g., menorrhagia, postpartum timing of IUD insertion] and category of the exposure [e.g., no recent menorrhagia diagnosis, 4 days to 6 weeks postpartum]). In this study population, uterine perforation risk appeared to be greatest for women with IUDs placed from 4 days to 6 weeks postpartum. Clinicians should be aware of this risk, and consideration should be given to delaying IUD insertion to a later postpartum time period. The results also suggest that IUD insertions done within the first 3 days after delivery are less likely to result in a uterine perforation than those done in later postpartum time periods (e.g., 4 days to 14 weeks postpartum) which also has clinical implications for optimal timing of insertions. Breastfeeding at the time of IUD insertion and a diagnosis of menorrhagia within the 12 months before IUD placement were also associated with higher risk of uterine perforation. LNG-IUDs also appeared to be associated with higher risk of uterine perforation than copper IUDs, but since Mirena, the most commonly used LNG-IUD, is indicated for women with menorrhagia, there is the potential for some residual confounding that should be further explored.

Overall, incidence of IUD expulsion (9 to 47 per 1,000 person-years, depending on the exposure and category of the exposure) was about 10-fold higher than incidence of uterine perforation. If unrecognized, complete IUD expulsion could result in unplanned pregnancy. IUD expulsions were most frequent with immediate postpartum placement (within 3 days postpartum), and these women should have follow-up in the postpartum period to assess expulsion. IUD expulsion was also higher among women with a diagnosis of menorrhagia within the previous 12 months, and counseling should be tailored to this population. Breastfeeding at the time of IUD insertion among those less than 52 weeks postpartum was associated with a lower risk of IUD expulsion. Compared with copper IUDs, LNG-releasing IUDs were also related to a lower risk of expulsion. The present study

might have overestimated risks related to partial IUD expulsions, as our definition of partial IUD expulsion was intentionally rather conservative and included malpositioned IUDs that were recognized on ultrasound and were replaced by the clinician.

Overall, in APEX IUD, the risk of uterine perforation was highest in women with IUD insertion 4 days to 6 weeks postpartum and among women who were ≤ 52 weeks postpartum and breastfeeding at the time of IUD insertion. The risk of IUD expulsion was highest in women with IUD insertion 0 to 3 days postpartum and among women with a recent diagnosis of menorrhagia. Clinicians should be aware of the higher risks of uterine perforation associated with IUD insertion during specific postpartum time periods and while women are breastfeeding and the higher risks of IUD expulsion with menorrhagia and immediate postpartum timing of IUD insertion and consider these factors while counseling their patients about IUD use.