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Incidence of opioid-managed pelvic pain after hysteroscopic sterilization versus laparoscopic sterilization, U.S. 2005-2012

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Abstract

Objective—Compare incidence of opioid-managed pelvic pain within 12-months after hysteroscopic and laparoscopic sterilization.

Methods—Using administrative claims, we identified women age 18-49 without recent history of childbirth who underwent hysteroscopic or laparoscopic sterilization between 2005-2012. We defined the outcome as ≥2 diagnoses for pelvic pain and ≥2 prescription fills for opioids. We calculated adjusted hazard ratios (HR) using Cox models and propensity score methods (matching and inverse-probability-of-treatment-weighting [IPTW]).

Results—We identified 71,875 eligible women (hysteroscopic n=26,927 [37.5%], laparoscopic n=44,948 [62.5%]). Of those, 236 (0.88%) hysteroscopic patients and 420 (0.93%) laparoscopic patients experienced the outcome (crude HR=0.97, [95%CI: 0.83, 1.14]). Adjusted analyses also yielded near-null results (matched HR=1.08 [95%CI: 0.90, 1.31]; IPTW HR=0.97 [95%CI: 0.80, 1.18]). While most sensitivity analyses generated results close to the null, hazard ratios estimated using propensity score matching ranged from 0.65 to 1.53.

Conclusions—Among women without recent history of childbirth, we did not find compelling evidence of a clinically meaningful increase in the incidence of pelvic pain requiring opioids

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during the year after hysteroscopic sterilization. However, effects observed in sensitivity analyses may merit further investigation.

Keywords

hysteroscopic sterilization; opioids; pelvic pain; laparoscopic sterilization; administrative claims

INTRODUCTION

Hysteroscopic sterilization is a relatively new alternative to laparoscopic sterilization, in which implanted coils prompt permanent occlusion of the fallopian tubes. Unlike laparoscopic sterilization, hysteroscopic sterilization requires no surgical incisions and is frequently completed in the outpatient setting. Media reports have described instances of prolonged abdominal/pelvic pain in women who underwent hysteroscopic sterilizations, prompting Bayer to add chronic pelvic pain as a long-term risk in the brochure for their hysteroscopic sterilization device, Essure® (Bayer, Morrisville, NC).[1,2] However, documented cases in the medical literature of chronic pelvic pain after hysteroscopic sterilization are rare.[3,4]

The hysteroscopic sterilization device contains an inner coil of stainless steel with polyethylene terephthalate (PET) fibers and an outer coil of titanium-nickel (nitinol).[5] The coil is placed into the interstitial portion of each fallopian tube under hysteroscopic guidance. Polyethylene fibers have long been used with success in other medical devices requiring tissue ingrowth such as arterial grafts.[6] Similar tissue response in the fallopian tubes ultimately results in tubal occlusion. Nickel allergy, chronic inflammation, and coil perforation or malposition are postulated mechanisms by which hysteroscopic sterilization could cause chronic abdominopelvic pain.[3,4,7]

Few studies have evaluated the risk of rare but serious adverse events after hysteroscopic sterilization.[4,8-10] Due to the large sample size needed, randomized controlled trials are unable to address rare pain events after hysteroscopic sterilization. The two studies that actively compare pain events between laparoscopic and hysteroscopic sterilization patients were both prospective cohort studies with fewer than 100 patients, insufficiently powered to evaluate rare outcomes.[9,10] Furthermore, neither evaluated outcomes beyond 90 days after sterilization. On October 18, 2013 the FDA responded to patient advocacy groups with a review stating that the currently limited evidence base does not link hysteroscopic sterilization to above-normal rates of pain or discomfort.[11]

Given the limited data available, there is a need for large-sample, population-based research evaluating pain outcomes after hysteroscopic sterilization. To address this evidence gap, we compared incidence of opioid-managed pelvic pain within 12 months in hysteroscopic and laparoscopic sterilization patients using data from a large healthcare claims database.

METHODS

Data Source

We used Truven Health's MarketScan Commercial Claims & Encounters Database (Copyright © 2013 Truven Health Analytics Inc.; all rights reserved) for the years 2005-2012, which contains de-identified healthcare and pharmaceutical claims for enrollees in over 150 large employer-provided insurance plans from across the United States. In the most recent year of data, it covered over 50 million lives.[12] Approximately 55% of the U.S. population (170.1 million people) had employment-based insurance in 2011.[13] These data, therefore, constitute a substantial portion of the U.S. population with employer-provided insurance.

Study Population

We identified a cohort of women ages 18-49 from inpatient and outpatient medical claims from 2005-2012 with current procedural terminology (CPT) codes for either hysteroscopic (CPT: 58565) or laparoscopic (CPT: 58670, 58671) sterilization. We did not include postpartum sterilizations since 1) we considered women with recent deliveries to be clinically unique and 2) we were concerned postnatal payment bundling may limit our ability to study these patients using claims data.

Though approved in 2002, hysteroscopic sterilization procedures cannot be reliably identified using administrative claims data until 2005 when unique codes for hysteroscopic sterilization were added to the Physician Fee Schedule.[14] Two hysteroscopic sterilization devices were marketed during the study period: Essure® (Bayer, Morrisville, NC) from 2005 to 2012 and Adiana® (Hologic, Bedford, MA) from 2009 to 2012. The CPT codes for hysteroscopic sterilization do not identify which device was placed.

In order to create a uniform time window to ascertain baseline covariate information (henceforth look-back), we restricted the cohort to women with six months of continuous enrollment before sterilization. We only included the first eligible procedure undergone by each woman and excluded women with claims for both sterilization procedures on the same day. Women were excluded if they had a claim for endometrial ablation on the same day or if their six-month history contained a claim related to childbirth, any diagnosis used in the outcome definition, or any prescription fill for opioids. For codes used to define study exclusions, see Web appendix 1. We assumed opioid prescriptions within 14 days of sterilization were routine medications directly related to the index procedure and did not use them to determine study eligibility or outcomes.

Outcomes

Starting follow up 14 days after sterilization, we evaluated opioid-managed pelvic pain using pharmaceutical claims and International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes associated with service claims. To qualify for the outcome, we required patients 1) have at least two diagnoses relating to pelvic pain, including dysmenorrhea (ICD-9: 625.3), abdominal pain (789.0x), or symptoms associated with female genital organs (ICD-9: 625.8 and 625.9) occurring on separate days during follow-

up, and 2) have at least two opioid prescriptions filled on separate days. Though the codes used in the outcome which refer to symptoms associated with female genital organs (ICD-9: 625.8, 625.9) may include non-pain symptoms, physicians frequently use them to code pelvic pain and prior research efforts (including the Agency for Health Research and Quality Clinical Classification Software) have used them accordingly.[15-17] We recorded the outcome date for each patient as the earliest date by which all outcome criteria were satisfied. Observations were censored when patients disenrolled (e.g. switched to an insurance plan not captured by MarketScan) or at the end of study follow-up (one year after sterilization).

Covariates

Covariates of interest included age at the time of sterilization, region-of-service and calendar year. We evaluated healthcare utilization variables in the six-month history, including any hospital admission and prior surgeries (identified using CPT codes for surgical anesthesia) and continuous variables for the number of prescription fills and outpatient visits. We used CPT and ICD-9 codes to identify relevant procedures (e.g., non-obstetric ultrasounds) and prevalent conditions (e.g., diabetes) in the patient's history. We considered all procedures and diagnoses present in >1% of either sterilization group, in addition to some less prevalent procedures and diagnoses which were of special clinical interest. For codes used to define study covariates, see Web Appendix 1.

Statistical Analyses

We compared baseline characteristics of laparoscopic and hysteroscopic sterilization patients and evaluated covariate imbalance between the sterilization groups for both categorical and continuous covariates using the standardized difference.[18]

We estimated the probability of each patient receiving hysteroscopic sterilization conditional on baseline covariates (also called the propensity score) using logistic regression.[19] Covariate distributions shifted over calendar time (e.g. hysteroscopic patients were more likely than laparoscopic patients to have pelvic organ prolapse, fibroids, and a history of inpatient hospital stay early in the study period, but were less likely to have them later in the study period). To account for changes in the channeling of patients to (or away from) this relatively novel procedure over the study period, propensity scores were estimated using calendar-year specific models.

We included covariates in propensity score models based on the plausibility and the magnitude of their association with opioid-managed pelvic pain. To evaluate the magnitude of covariate-outcome relationships, we used Cox proportional hazard models within treatment groups. Final propensity score models included age, obesity, diabetes, excessive/frequent menstruation, polycystic ovary syndrome (PCOS), chronic obstructive pulmonary disease (COPD), any inpatient admission, prior surgery, as well as the number of outpatient visits and the number of distinct prescriptions in the patient's six-month history.

We used two propensity score adjustment methods: 1) propensity score matching and 2) stabilized inverse-probability-of-treatment-weighting (IPTW).[20] Both propensity score matching and IPTW methods control confounding by balancing the distribution of measured

covariates across treatment groups. We formed propensity score matched pairs within calendar years using a 1-to-1 greedy matching algorithm with a maximum caliper of 0.1.[21]

We compared the baseline characteristics of the matched and weighted cohorts by sterilization type to ensure balance of measured covariates of interest. Cox proportional hazards regression models were used to estimate adjusted hazard ratios and 95% confidence intervals for the effect of sterilization type on opioid-managed pelvic pain, accounting for censoring. We compared the cumulative incidence of opioid-managed pelvic pain at 2, 4, 6, 8, 10, and 12 months post-sterilization between treatment groups for the crude, IPTW, and matched analyses using Kaplan-Meier survival curves.

We conducted seventeen sensitivity analyses, including analyses varying the outcome definition (SA 1-8), perioperative period (SA 9-12), and look-back (SA 14-15), which are described in detail in Web appendix 2. We also conducted two stratified analysis, one evaluating effect estimates by quartiles (defined within calendar year) of the propensity score and a second evaluating effect estimates within discrete windows during follow-up.

This study was reviewed by University of North Carolina's institutional review board (study #: 13-2445) and found to be exempt. We conducted all analyses using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

We identified a total of 71,875 eligible women who underwent either a laparoscopic or hysteroscopic sterilization procedure between 2005 and 2012 (Figure 1). Of these, 26,927 (37.5%) were hysteroscopic sterilizations and 44,948 (62.5%) were laparoscopic. Overall, 656 (0.91%) women experienced the outcome of opioid-managed pelvic pain including 236 (0.88%) women in the hysteroscopic group and 420 (0.93%) women in the laparoscopic group. The mean (median) follow-up times were 275 (365) days among hysteroscopic sterilization patients and 283 (365) days among laparoscopic sterilization patients.

Table 1 describes the characteristics of laparoscopic and hysteroscopic patients in the crude, propensity score matched analysis, and IPTW analyses. Though the hysteroscopic cohort was slightly older than the laparoscopic cohort, age distributions were similar between the sterilization groups. Compared to laparoscopic sterilization, hysteroscopic sterilization patients more often had a history of excessive or frequent menstruation and less often had a history of ovarian cysts or absence of menstruation. The hysteroscopic sterilization group had greater use of non-obstetric ultrasounds and depot medroxyprogesterone acetate (DMPA), an injectable long-term contraceptive, before sterilization. The mean number of prescriptions filled during the baseline period was higher among hysteroscopic patients. The propensity score matched analysis was comprised of 50,986 subjects, including 25,493 (95%) hysteroscopic sterilization patients. In matched and IPTW analyses, all modeled covariates (i.e. those that impacted the outcome) were balanced between the sterilization groups (standardized differences ≤ 0.01).

In the crude analysis, the one-year incidence of opioid-managed pelvic pain was approximately equal among hysteroscopic and laparoscopic (referent) patients (HR=0.97,

95%CI 0.83–1.14). The crude cumulative incidence was greater in the hysteroscopic sterilization patients at six months but not at one year (Figure 2A and Web appendix 3). At six months, the cumulative incidence was 0.48% (95%CI 0.40%–0.58%) in hysteroscopic patients and 0.40% (95%CI 0.34%–0.47%) in laparoscopic patients. At 12 months, it reached 1.22% (95%CI 1.07%–1.38%) and 1.29% (95%CI 1.17%–1.41%) in hysteroscopic and laparoscopic patients, respectively.

The effect estimate under the IPTW analysis was similar to the crude estimate (HR=0.97, 95%CI 0.80–1.18), while the propensity score matched analysis (HR=1.08, 95%CI 0.90–1.31) indicated marginally increased risk in hysteroscopic sterilization patients. In the IPTW analysis, the mean stabilized weight was 1.00 in both the laparoscopic and hysteroscopic sterilization groups.

The IPTW Kaplan-Meier analysis indicated that cumulative incidence did not differ by sterilization status throughout the study period. The propensity score matched cumulative incidence in the hysteroscopic group was slightly higher over the course of the study period, though this was not significantly different from the laparoscopic group (Figure 2B and Web appendix 3). At six months, cumulative incidence reached 0.48 (95%CI 0.39%–0.58%) in the hysteroscopic group and 0.38% (95%CI 0.30%–0.47%) in the laparoscopic group. At 12 months, it reached 1.23% (95%CI 1.08%–1.41%) and 1.17% (95%CI 1.02%–1.34%) in hysteroscopic and laparoscopic patients, respectively.

The crude, IPTW and propensity score matched results of the sensitivity analyses are presented in Figure 3. Nearly all sensitivity analyses indicate no difference in the risk of opioid-managed pelvic pain between the sterilization groups. Two notable exceptions were the analysis in which we required 30 days supply of opioids in the outcome definition (SA 4) and the sensitivity analysis in which we used up to five years of available pre-exposure claims history to define study covariates and exclusion criteria (SA 15). The use of the more specific outcome definition produced protective effects (HR=0.65, 95%CI 0.41–1.03) while the extended look-back period suggested an increased risk in the hysteroscopic group (HR=1.53, 95%CI 1.11–2.11). Combining the two analyses (SA 17) yielded results close to the null (HR=0.93, 95%CI 0.46–1.87).

In the stratified analysis estimating effects within quartiles of the propensity score distribution, the estimated hazard ratio was 0.96 (95%CI 0.71–1.29) in the first quartile, 1.21 (95%CI 0.89–1.66) in the second quartile, 0.88 (95%CI 0.60–1.29) in the third quartile, and 0.96 (95%CI 0.71–1.30) in the fourth quartile among 5,407, 6,486, 7,077, and 7,957 hysteroscopic patients respectively. The results of the analysis evaluating effects within discrete windows during follow-up (Web appendix 4) indicate possible increased risk of opioid-managed pelvic pain among hysteroscopic patients in time periods more proximal to sterilization (not counting first 14 days) that diminishes in more distal time periods.

DISCUSSION

Among women without a recent history of childbirth, we report a non-significant 8% increase (HR=1.08, 95%CI 0.90–1.31, p=0.42) in the hazard of opioid-managed pelvic pain

over 12 months of follow-up in patients sterilized hysteroscopically versus laparoscopically. Given the low prevalence of the outcome, an effect of this magnitude is clinically inconsequential. Given that hysteroscopic sterilization represented 50% of all sterilizations in the most recent year of these data (2012), evaluating the relative safety of this method is an important public health issue.

Only two prior studies have compared pain outcomes in laparoscopic and hysteroscopic sterilization patients, both of which were prospective studies based on patient surveys.[9,10] The sample size in this study (26,927 hysteroscopic and 44,948 laparoscopic) is substantially larger those of Syed et al.[10] and Duffy et al.[9], which included fewer than 150 patients combined. While both studies reported fewer pain events among hysteroscopic sterilization patients, neither enrolled sufficient numbers of patients to evaluate the effect of sterilization type on rare outcomes. One had a follow-up of four weeks[10] and the other 90 days[9], which would make the present study's follow-up substantially longer than the existing literature. However, the present study could only evaluate an opioid-managed pain proxy and the two prospective studies were better able to assess pain using patient surveys.

In general, the effect estimates from the matched analysis were more likely to suggest greater risk for hysteroscopic patients than the results of the IPTW analysis. Dissimilarity between hazard ratios estimated in the propensity score matched and IPTW analyses may be due to the fact that they estimate different effects in the presence of treatment effect heterogeneity.[22,23] However, sample size considerations limit our ability to fully explore whether there are sources of effect heterogeneity present.

One limitation of these data is that pharmaceutical claims do not include the clinical indication for the prescription, so we investigated whether other conditions (unrelated to the device) may have occurred during follow up that would account for differences in opioid utilization between the two groups. In comparing other pain-related diagnoses among women who had the event, we found that fibroid diagnoses occurred more frequently during follow-up among hysteroscopic patients (20%) than among laparoscopic patients (13%). This difference may partially explain the greater opioid use observed in the hysteroscopic group. In a sensitivity analysis (SA 3) requiring opioid prescriptions to occur within a week following pelvic pain diagnoses, we found no difference between the groups (HR=1.03, 95%CI 0.75–1.43).

Our objective was to evaluate long-term pelvic pain rather than acute post-procedure pain. However, from a patient perspective, being able to compare the risk of opioid-managed pelvic pain any time during the year after the procedure, including the immediate post-operative period may also be important. In a sensitivity analysis (SA 10) that counted all post-procedure opioid use toward the outcome we found no effect (HR=1.01, 95%CI 0.85–1.21).

In the sensitivity analysis that allowed up to five years of history (SA 15), the results of the IPTW analysis (HR=1.15, 95%CI 0.87–1.52) and the matched analysis (HR=1.53, 95%CI 1.11–2.11) were further from the null than those of the primary analysis. A recent simulation study reported that an all-available approach to covariate measurement led to less bias than

using a six-month history for all subjects.[24] However, the relevance of these findings is uncertain when the treatment populations are changing composition over time or when the all-available history is used to define criteria for exclusion, both of which are the case in this analysis. Furthermore, while this result is potentially important, the absolute difference in risk is small due to the rare outcome.

This study has several limitations. First, there may be important unmeasured variables that result in residual confounding in the relationship between sterilization and opioid-managed pain outcomes (e.g. BMI). Second, opioid-managed pelvic pain is only a proxy for true pain outcomes and is likely limited in both sensitivity and specificity. Validated instruments measuring pain/discomfort exist but are impractical in studies with very large sample sizes. We conducted multiple sensitivity analyses to explore alternative outcome definitions, none of which indicated elevated risk in the hysteroscopic sterilization group. Third, in our primary analysis we restricted evaluation of baseline covariates and exclusions for patient histories with evidence of the outcome-of-interest to a six-month look-back period, which may result in under-ascertainment of relevant covariates and residual confounding. Fourth, this study only evaluated outcomes up to one year following sterilization. Fifth, by studying pharmaceutical claims we assume that a prescription fill implies medication use, which may not be the case. However, we sought to reduce this misclassification by requiring two opioid prescriptions for the outcome. Finally, the employer-provided insurance plan enrollees studied may limit generalizability since they may differ slightly from the general population in health status and healthcare utilization. However they are a stably insured population, enabling longitudinal research not possible with conventional data sources.

This study has multiple strengths. Using administrative claims data enables analysis of a large sample needed to evaluate rare outcomes. To our knowledge, this is the largest study to date evaluating adverse events after hysteroscopic sterilization. Furthermore, exposure ascertainment was both highly sensitive and highly specific. Finally, we conducted extensive sensitivity analyses to evaluate the effect of sterilization type on pain outcomes under a variety of assumptions and outcome definitions. With the exception of the analysis that included all available claims history (up to five years), none of the sensitivity analyses indicated increased incidence of opioid-managed pelvic pain in hysteroscopic sterilization patients.

Though expensive and logistically difficult to implement due to the low incidence of the outcome, future studies able to ascertain pain endpoints with greater sensitivity and specificity would be helpful in clarifying the relationship between sterilization type and chronic pain events. Furthermore, research is still needed which evaluates other adverse events unrelated to pain (e.g., bleeding outcomes) that have been reported by patients who have undergone recent hysteroscopic sterilization.

Through the use of administrative claims data, we were able to evaluate the incidence of a rare but serious outcome following sterilization in over 70,000 women from a national, population-based sample over an eight-year period. We found a small but not clinically or statistically significant increase in the incidence of pelvic pain requiring opioid-management during the 12 months after hysteroscopic versus laparoscopic sterilization. Given that

hysteroscopic sterilization represented 50% of sterilizations in 2012 and is likely to increase in use, further research is needed to address concerns about adverse events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Bayer, AG. [November 30, 2013] Essure permanent birth control: Warnings, precautions and other potential risks. Available at: http://www.essure.com/what-is-essure/warnings-precautions-other-potential-risks.
2. Deardorff, J. Women report complications from Essure birth control. Chicago Tribune; Dec 22. 2013 Available at: http://articles.chicagotribune.com/2013-12-22/health/ctessure-safety-met-20131222_1_essure-conceptus-fallopian-tubes. [June 26, 2014]
3. Povedano B, Arjona J, Velasco E, et al. Complications of hysteroscopic Essure® sterilisation: Report on 4306 procedures performed in a single centre. BJOG. 2012; 1197:795–799. DOI: 10.1111/j.1471-0528.2012.03292.x. [PubMed: 22360159]
4. Langenveld J, Veersema S, Bongers MY, et al. Tubal perforation by Essure: Three different clinical presentations. Fertil Steril. 2008; 905:2011.e5–2011.e10. DOI: 10.1016/j.fertnstert.2008.06.020. [PubMed: 18692813]
5. Valle RF, Carignan CS, Wright TC. Tissue response to the STOP microcoil transcervical permanent contraceptive device: results from a prehysterectomy study. Fertil Steril. 2001; 765:974–980. PubMed: 11704120. [PubMed: 11704120]
6. Estridge TD, Feldman DS. Quantification of vascular ingrowth into dacron velour. J Biomater Appl. 1991; 62:157–169. PubMed: 1838122. [PubMed: 1838122]
7. Jansen NE, Vleugels MP, Kluivers KB, et al. Bilateral cornual abscess after endometrial ablation following Essure sterilization. J Minim Invasive Gynecol. 2007; 144:509–511. PubMed: 17630173. [PubMed: 17630173]
8. Panel P, Grosdemouge I. Predictive factors of Essure implant placement failure: prospective, multicenter study of 495 patients. Fertil Steril. 2010; 931:29–34. DOI: 10.1016/j.fertnstert.2008.09.063. [PubMed: 19022435]
9. Duffy S, Marsh F, Rogerson L, et al. Female sterilisation: a cohort controlled comparative study of ESSURE versus laparoscopic sterilisation. BJOG. 2005; 11211:1522–1528. PubMed: 16225573. [PubMed: 16225573]
10. Syed R, Levy J, Childers ME. Pain associated with hysteroscopic sterilization. JSLS. 2007; 111:63. PubMed: 17651558. [PubMed: 17651558]

11. [October 18, 2013] Essure permanent birth control: FDA's review of reported problems. Oct 18. 2013 Available at: http://www.fda.gov/medicaldevices/productsandmedicalprocedures/implantsandprosthetics/ucm371014.htm.
12. Hansen, L.; Chang, S. [June 20, 2014] Health research data for the real world: The Thomson Reuters MarketScan databases. white paper, 2011. 2011. Available at: http://www.truvenhealth.com/assets/2012_Truven_MarketScan_white_paper.pdf.
13. DeNavas-Walt, C.; Proctor, BD.; Smith, JC. [June 20, 2014] US Census Bureau, current population reports, P60-243, income, poverty, and health insurance coverage in the United States: 2011. Available at: http://www.census.gov/prod/2012pubs/p60-243.pdf.
14. Witt M. Four CPT gems for 2005. OBG Management. 2005; 171:36.
15. Elixhauser, A.; Steiner, C.; Palmer, L. [April 10, 2014] Healthcare cost and utilization project (HCUP) clinical classification software - U.S. Agency for Healthcare Research and Quality. Available at: www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp.
16. Anger JT, Litwin MS, Wang Q, et al. Variations in stress incontinence and prolapse management by surgeon specialty. J Urol. 2007; 1784:1411–1417. PubMed: 17706713. [PubMed: 17706713]
17. Anger JT, Rodriguez LV, Wang Q, et al. The role of provider volume on outcomes after sling surgery for stress urinary incontinence. J Urol. 2007; 1774:1457–1462. PubMed: 17382752. [PubMed: 17382752]
18. Yang D, Dalton J. A unified approach to measuring the effect size between two groups using SAS®. SAS Global Forum. 2012:335–2012.
19. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983; 701:41–55.
20. Cole SR, Hernán MA. Adjusted survival curves with inverse probability weights. Comput Methods Programs Biomed. 2004; 751:45–49. PubMed: 15158046. [PubMed: 15158046]
21. Parsons L. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. SUGI. 2001:214–26.
22. Imbens GW. Nonparametric estimation of average treatment effects under exogeneity: a review. Rev Econ Stat. 2004; 861:4–29.
23. Stürmer T, Rothman KJ, Glynn RJ. Insights into different results from different causal contrasts in the presence of effect-measure modification. Pharmacoepidemiol Drug Saf. 2006; 1510:698–709. PMID: 16528796. [PubMed: 16528796]
24. Brunelli SM, Gagne JJ, Huybrechts KF, et al. Estimation using all available covariate information versus a fixed look-back window for dichotomous covariates. Pharmacoepidemiol Drug Saf. 2013; 225:542–550. DOI: 10.1002/pds.3434. [PubMed: 23526818]

Key-points

1. This is believed to be the largest study to date evaluating adverse events after hysteroscopic sterilization.
2. This study provides an active comparison of hysteroscopic and laparoscopic sterilization, which are uncommon in the adverse events literature.
3. We used two propensity score methods to reduce bias in effect estimates obtained using administrative claims data.
4. We did not find compelling evidence of a clinically important increase in incidence of pelvic pain requiring opioid-management during the 12 months after hysteroscopic versus laparoscopic sterilization.
5. Findings do not raise concern for increased risk of opioid-managed pelvic pain in hysteroscopic sterilization patients, though effects observed in some sensitivity analysis (ranging from HR=0.65 to 1.53) may merit further investigation.

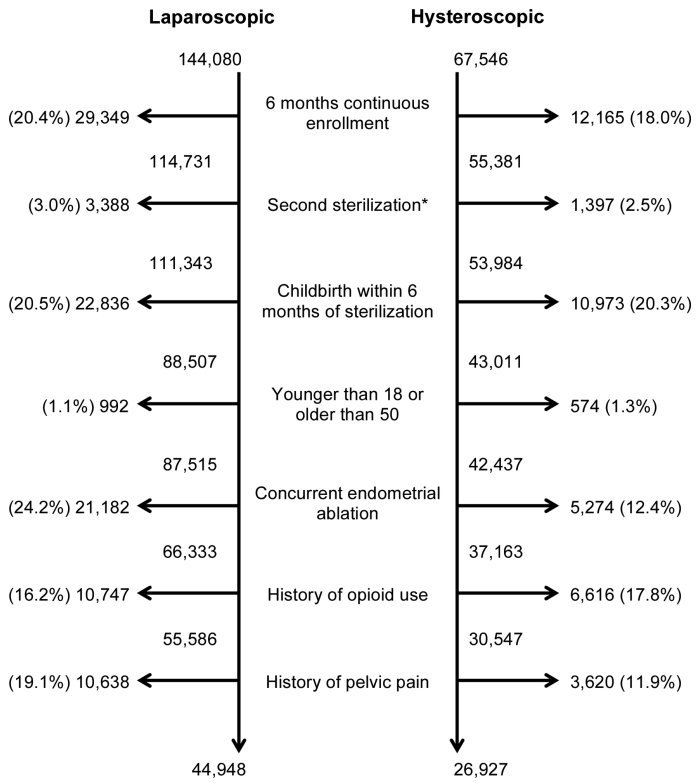

Figure 1.

Study exclusions.

* Patients were excluded if they had two sterilizations on the same index sterilization date. Patients were also excluded if they had a sterilization in their six-month history which did not qualify as an index sterilization due to a lack of six-month continuous enrollment before the service date. In the case that a woman had a second sterilization in follow-up, only the first sterilization was counted as an index sterilization in the analysis.

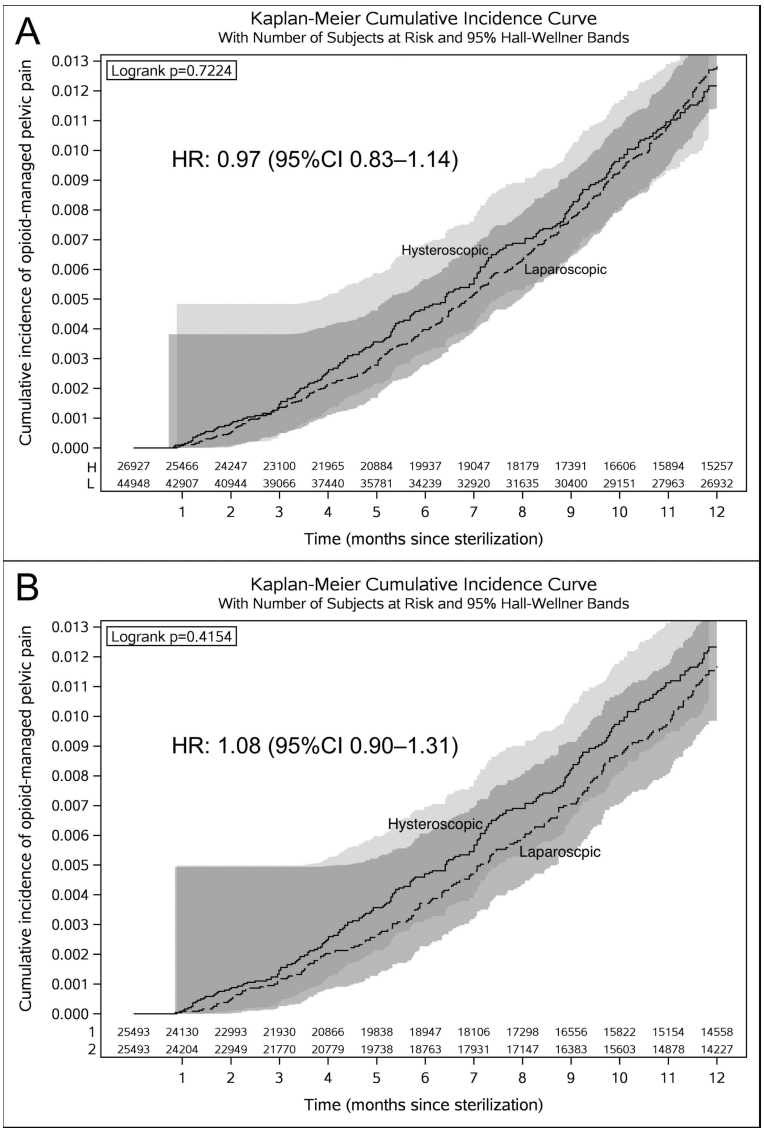

Figure 2.

12-month cumulative incidence of opioid-managed pelvic pain with 95% Hall-Wellner confidence bands and number of women at risk in A) the crude cohort and B) the propensity score matched cohort.

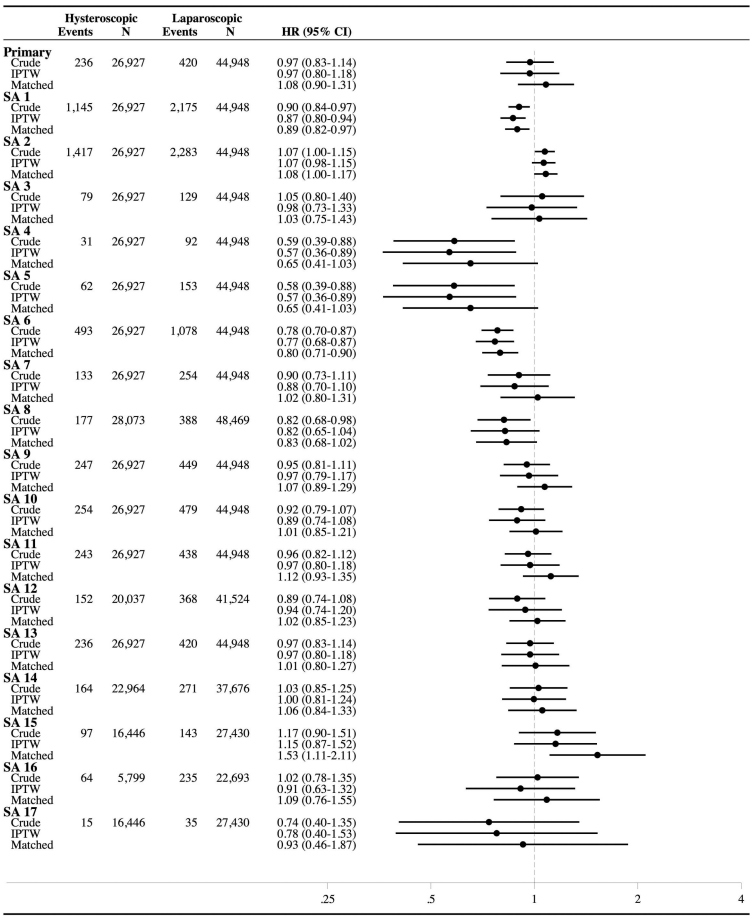

Figure 3.

Forest plot of hazard ratio estimates from sensitivity analyses.

SA 1: outcome definition requiring two pelvic-pain diagnoses (no prescription requirement), SA 2: outcome definition requiring two opioid prescription fills (no diagnosis requirement), SA 3: two instances of a pelvic pain diagnosis occurring within a week before an opioid prescription fill, SA 4: outcome definition requiring two pelvic pain diagnoses and a cumulative 30 days supply of opioids, SA 5: outcome definition requiring one pelvic-pain diagnosis and a cumulative 30 days supply of opioids, SA 6: outcome definition requiring one inpatient or ED pelvic pain diagnosis, SA 7: outcome definition requiring one inpatient or ED pelvic pain diagnosis and two opioid fills, SA 8: outcome definition including only 625.3 (dysmenorrhea) and 789.0x (abdominal pain), SA 9: perioperative period for procedure-related opioids from -14 to +7 days, SA 10: perioperative period for procedure-related opioids from -14 to 0 days, SA 11: no perioperative period for procedure-related pain diagnoses, SA 12: perioperative period for procedure-related opioids from 0 to +14 days, SA 13: included a term for region-of-service in propensity score models, SA 14: require 12 months of continuous enrollment before index sterilization date, instead of six, SA 15: allow up to five years of available look-back prior to sterilization (6 months continuous still required), SA 16: restrict cohort to years when only Essure was on the Market (2005-2008),

SA 17: allow up to five years of look-back and use outcome requiring 30 days supply of opioids and two pelvic pain diagnoses (combines SA 4 and SA 15).

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Table 1

Balance of study covariates in crude, inverse-probability-of-treatment weighted, and propensity score matched cohorts.

	Crude Analysis					IPTW Analysis			Matched Analysis		
	Hyst. N=26,927		Lap. N=44,948			Hyst. N=26,936	Lap. N=44,945.2		Hyst. N=25,580	Lap. N=25,580	
	N	Prop	N	Prop	StdzDiff	Prop	Prop	StdzDiff	Prop	Prop	StdzDiff
AGE											
Mean (SD)	37.8 (5.4)		36.6 (5.7)		0.23	37.0 (5.7)	37.0 (5.6)	0.00	37.6 (5.4)	37.5 (5.3)	0.03
18-24	205	0.01	929	0.02	−0.11	0.02	0.02	0.00	0.01	0.01	0.00
25-29	1,748	0.06	4,577	0.10	−0.13	0.09	0.09	0.00	0.07	0.07	−0.01
30-34	5,286	0.20	10,288	0.23	−0.08	0.22	0.22	0.00	0.20	0.21	−0.01
35-39	8,752	0.33	14,338	0.32	0.01	0.32	0.32	0.00	0.33	0.34	0.00
40-44	7,916	0.29	11,266	0.25	0.10	0.27	0.27	0.00	0.29	0.28	0.01
45-49	3,020	0.11	3,550	0.08	0.11	0.09	0.09	0.00	0.10	0.09	0.01
REGION*											
Northeast	3,283	0.12	6,109	0.14	−0.04	0.12	0.15	−0.08	0.12	0.16	−0.12
North Central	7,936	0.29	10,514	0.23	0.14	0.30	0.23	0.15	0.29	0.23	0.14
South	11,232	0.42	20,965	0.47	−0.10	0.41	0.45	−0.08	0.42	0.44	−0.04
West	4,066	0.15	6,722	0.15	0.00	0.16	0.15	0.02	0.15	0.15	0.00
Unknown	410	0.02	638	0.01	0.01	0.01	0.02	−0.02	0.02	0.02	−0.03
CALENDAR YEAR*											
2005	395	0.01	6,140	0.14	−0.47	0.09	0.09	0.00	0.02	0.02	0.00
2006	945	0.04	5,492	0.12	−0.33	0.09	0.09	0.00	0.04	0.04	0.00
2007	1,641	0.06	5,581	0.12	−0.22	0.10	0.10	0.00	0.06	0.06	0.00
2008	2,818	0.10	5,480	0.12	−0.05	0.12	0.12	0.00	0.11	0.11	0.00
2009	4,445	0.17	5,627	0.13	0.11	0.14	0.14	0.00	0.17	0.17	0.00
2010	5,152	0.19	5,206	0.12	0.21	0.14	0.14	0.00	0.18	0.18	0.00
2011	5,802	0.22	5,701	0.13	0.24	0.16	0.16	0.00	0.21	0.21	0.00
2012	5,729	0.21	5,721	0.13	0.23	0.16	0.16	0.00	0.21	0.21	0.00
RX: Opiate fill between −14 and +14 days*†	10,462	0.39	25,549	0.57	−0.37	0.36	0.57	−0.43	0.39	0.58	−0.39
Excessive or frequent menstruation	2,120	0.08	2,052	0.05	0.14	0.06	0.06	0.00	0.06	0.06	0.01

	Crude Analysis					IPTW Analysis			Matched Analysis		
	Hyst. N=26,927		Lap. N=44,948			Hyst. N=26,936	Lap. N=44,945.2		Hyst. N=25,580	Lap. N=25,580	
	N	Prop	N	Prop	StdzDiff	Prop	Prop	StdzDiff	Prop	Prop	StdzDiff
Absence of menstruation*	883	0.03	2,107	0.05	−0.07	0.03	0.05	−0.06	0.03	0.04	−0.06
Fibroids*	617	0.02	1,069	0.02	−0.01	0.02	0.03	−0.04	0.02	0.03	−0.04
Ovarian cysts*	655	0.02	1,637	0.04	−0.07	0.02	0.04	−0.11	0.02	0.04	−0.10
Polycystic Ovary Syndrome (PCOS)	130	0.00	194	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00
Pelvic organ prolapse*	162	0.01	338	0.01	−0.02	0.01	0.01	−0.02	0.01	0.01	−0.03
Obesity	835	0.03	1,295	0.03	0.01	0.03	0.03	0.00	0.03	0.03	0.01
Diabetes mellitus	688	0.03	1,079	0.02	0.01	0.02	0.02	0.00	0.02	0.02	0.00
Chronic obstructive pulmonary disorder	65	0.00	127	0.00	−0.01	0.00	0.00	0.00	0.11	0.12	−0.01
Ultrasound (non-obstetric)*	3,259	0.12	4,679	0.10	0.05	0.11	0.11	−0.02	0.09	0.02	0.30
Depot medroxyprogesterone acetate (DMPA)*†	2,426	0.09	1,138	0.03	0.28	0.09	0.02	0.30	0.02	0.02	0.00
Any inpatient stay	476	0.02	1,106	0.02	−0.05	0.02	0.02	0.00	0.01	0.01	0.00
Prior surgeries	174	0.01	328	0.01	−0.01	0.01	0.01	0.00	0.00	0.00	0.00
	Mean	***(SD)***	***Mean***	***(SD)***	***StdzDiff***	***Mean (SD)***	***Mean (SD)***	***StdzDiff***	***Mean (SD)***	***Mean (SD)***	***StdzDiff***
Number of outpatient visits	5.76	(5.65)	5.90	(5.39)	−0.02	5.95 (6.52)	5.87 (5.25)	0.01	5.78 (5.63)	5.71 (4.96)	0.01
Number of prescription fills	4.26	(5.63)	3.89	(5.49)	0.07	4.04 (5.39)	4.04 (5.70)	0.00	4.08 (5.39)	4.03 (5.65)	0.01

Hyst=hysteroscopic, Lap=laparoscopic, IPTW=inverse-probability-of-treatment weighted, Prop=proportion, StdzDiff=standardized difference

*not included in propensity score models

†not eligible for inclusion in propensity score models (expected to act as an instrument of the sterilization type