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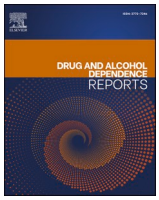

The risk of opioid use disorder among women undergoing obstetric-related procedures: Results from the Cerner Real-World Database

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HIGHLIGHTS

- Delivery modes significantly impact opioid use disorder risks.
- Induced abortion and miscarriage show the highest predicted OUD rates.
- Induced abortion yields the highest OUD odds vs. vaginal delivery.
- Cesarean leads in new opioid prescriptions vs. vaginal delivery.
- Ectopic pregnancy and abortion top in persistent opioid use risk.

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ABSTRACT

Introduction: While the relationship between various obstetric procedures and the onset of opioid use disorder (OUD) remains ambiguous, this study aims to elucidate the immediate and prolonged risks of OUD in women who have undergone procedures such as vaginal and cesarean deliveries, induced abortions, and treatments related to miscarriages and ectopic pregnancies.

Methods: Retrospective data ($n = 632{,}872$) from the Cerner Real-World Data™ for pregnant females (age 15–44) between January 2010 and March 2020 were used. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were used to compare odds of OUD for each obstetric outcome to normal vaginal delivery using multivariable logistic regression. New opioid prescriptions and persistent opioid prescriptions were secondary outcomes for which modified Poisson regression models were used.

Results: Compared to patients with a vaginal delivery, those with an ectopic pregnancy, a cesarean delivery, miscarriage, and an induced abortion had 84%, 46%, 119%, and 131% significantly higher odds of OUD (aOR [95% CI]: 1.84 [1.36, 2.48], 1.46 [1.29, 1.65], 2.19 [1.94, 2.47], and 2.31 [1.80, 2.96]) respectively. Among opioid naïve patients, all other obstetric procedure groups (besides miscarriage) had significantly higher risk of being prescribed new opioids than those with a vaginal delivery. Among those newly prescribed opioids, patients from all other obstetric procedure groups demonstrated a significantly higher risk of persistent opioid prescription compared to those who had a vaginal delivery.

Conclusion: The association between specific obstetric outcomes, notably miscarriage and induced abortions, and opioid use patterns should inform safer and more effective pain management in a maternal population.

1. Introduction

Globally, pregnancy and childbirth are significant life events that often require medical interventions. Obstetric and gynecological procedures, including cesarean deliveries, are among the most common surgical procedures worldwide. Pain management during and after these procedures is a critical component of care, with opioids often being prescribed for pain relief. However, the global opioid crisis has raised concerns about the potential risks associated with opioid prescriptions, especially among women of childbearing age.

In the United States, more than 5 million pregnancies occur each year, with an estimated 64% resulting in live births, 18% ending in

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induced abortions, and 17% terminating in fetal losses, which comprise miscarriages, ectopic pregnancies, and stillbirths (Curtain et al., 2013; Maddow-Zimet and Kost, 2021). Nearly all these outcomes require medical intervention making pregnancy and childbirth the most frequently reported reason for hospitalization in the country (Torio et al., 2013). Guidelines from the American College of Obstetricians and Gynecologists (ACOG) recommend a stepwise multimodal approach to pain management dependent on the mode of delivery. In the case of vaginal and cesarean deliveries, ACOG suggests that pain management should start with non-opioid medications, with opioids being reserved for more severe pain (ACOG, 2021). Current estimates indicate that approximately 28.5% of women who deliver vaginally and 75.7% of those who undergo cesarean sections in the US receive an opioid prescription shortly after delivery (Peahl et al., 2019; Prabhu et al., 2018). These rates are concerning, especially in light of evidence suggesting that surgical procedures involving opioids can lead to future persistent opioid use (Brummett et al., 2017; Jivraj et al., 2020; Karamchandani et al., 2020).

Recognizing the global implications of the opioid epidemic and the specific challenges faced by the US, it is crucial to understand the association between obstetric treatments and procedures and subsequent long-term opioid use or dependence. While the current opioid crisis in the US has been largely fueled by prescription opioids, illicit substances like heroin and fentanyl have also played a significant role. Specific subgroups, such as those receiving treatments for miscarriages and induced abortions, remain understudied (Bateman et al., 2016; Peahl et al., 2019). Our research aims to address this gap by exploring the immediate and long-term risk of opioid use disorder (OUD) among women undergoing various obstetric-related procedures. In doing so, our study seeks to provide insights that are relevant not only to the US but also to the broader global community, considering both prescription opioid exposure and the wider risks associated with OUD.

2. Methods

2.1. Settings and participants

This retrospective study utilized data from Cerner Real-World Data™ (CRWD), provided by the Cerner Health Corporation and subsequently acquired by Oracle. The CRWD database comprises longitudinal, de-identified electronic health records (EHRs). Data in Cerner Real-World Data is extracted from the EMR of hospitals in which Cerner has a data use agreement. Encounters may include pharmacy, clinical and microbiology laboratory, admission, and billing information from affiliated patient care locations. All admissions, medication orders and dispensing, laboratory orders and specimens are date and time stamped, providing a temporal relationship between treatment patterns and clinical information. Cerner Corporation has established Health Insurance Portability and Accountability Act-compliant operating policies to establish de-identification for Cerner Real-World Data. (Ehwerhemuepha et al., 2022). As of April 2022, CRWD contained records of nearly 100 million unique patients from 122 U.S. health systems, amounting to approximately 1.5 billion encounters.

Patients were included into the analysis if they were female, between the ages of 15 to 44, with known demographics (age, race, marital status, one digit zip-code, insurance), had a qualifying *International Statistical Classification of Diseases and Related Health Problems, Ninth/Tenth Revision* (ICD-9/10) or *Systematized Nomenclature of Medicine - Clinical Terms* (SNOMED-CT) code for pregnancy, had a following *Current Procedural Terminology* (CPT)/ICD/SNOMED-CT code for pregnancy ending (obstetric outcome) with normal vaginal delivery, cesarean delivery, ectopic pregnancy, miscarriage, or induced abortion (for patients with multiple, the first was used), and had obstetric outcomes between January 2010 and March 2020. Patients were excluded if they had an OUD any time prior to obstetric outcome or <30 days after (to account for possibly undiagnosed prior OUD being captured after obstetric outcome). Additionally, patients who had possible indications of OUD (having any of the codes used for classification but not meeting the requirements of the classification algorithm for OUD) prior to obstetric outcome or <30 days after were excluded from analysis. Finally, patients were excluded if they had been prescribed any opioids from two years to 8 days before obstetric outcome (the extra window before obstetric outcome accounted for some patients receiving pre-treatment pain prescriptions) and thus patients were required to be opioid naïve. After obstetric outcome all patients were followed for two years to look for primary/secondary outcomes, and thus patients included in March 2020 had the ability to obtain a full two years of follow-up with the data refresh ending in April 2022. To account for the impact of the coronavirus disease (COVID-19) on patients, a sensitivity analysis restricted inclusion from January 1, 2010 to December 31, 2017 so that with a full two years of follow-up (ending on December 31, 2019), no data from January 1, 2020 and on would be included.

2.2. Outcomes

The primary outcome of interest, among those opioid naïve and those with no history of OUD or OUD <30 days post obstetric outcome, was OUD (yes/no) >=30 days post obstetric outcome and up to two years later. OUD was defined by first gathering qualifying ICD-9/10, SNOMED, *Healthcare Common Procedure Coding System* (HCPCS), and *National Drug Code* (NDC) codes (Supplemental Table 5) and then using methodology adapted from the *Centers for Medicare & Medicaid Services* (CMS) *Chronic Condition Warehouse* (CCW) algorithm. Patients were defined as having OUD if they 1) had a qualifying ICD-9/10 or SNOMED diagnosis/procedure code on an inpatient or emergency encounter 2) had at least two diagnosis or procedure codes (or one of each) from any encounter type or 3) had a qualifying HCPCS or NDC code for opioid medication-assisted treatment (MAT). From all these qualifying conditions, the first date was used as the first date of OUD. It should be noted that this OUD definition can encompass disorders resulting from both prescription opioids and illicit opioids like heroin and fentanyl, given the comprehensive nature of the diagnostic codes utilized. Any patients that had any of the above codes but did not meet the criteria of the OUD inclusion methodology were removed from analysis.

Secondary outcomes, as adapted from previous studies (Brummett et al., 2017; Peahl et al., 2019; Wall-Wieler et al., 2020), were new and persistent prescription of opioids. Opioids were identified by NDC and Multum MediSource Lexicon (MMSL) drug codes (Cerner, 2020). These codes are displayed in Supplemental Table 6a–6c. Medications were required to have an order status of “active” or “complete” and medications with a designation of “as needed” were not included. New prescription (yes/no) was defined as receiving at least one prescription of opioids one week before to one week after obstetric outcome. This specifically pertains to prescription opioids and does not factor in any illicit opioid use. Again, the window before was allowed to account for some patients receiving pre-treatment pain prescriptions as well as the window after to account for patients receiving slightly delayed prescriptions. Among those with new opioid prescriptions, persistent prescription (yes/no) was defined as receiving opioid prescriptions 8 to 90 days post obstetric outcome as well as 91 to 365 days post obstetric outcome. Again, these outcomes were only searched among those who were opioid naïve and had no prior history of OUD or OUD <30 post obstetric outcome.

2.3. Predictors

The primary predictor of interest was the type of obstetric outcome, consisting of normal vaginal delivery, cesarean delivery, ectopic pregnancy, miscarriage, or induced abortion (categorical variable with five levels). These were identified by qualifying ICD-9/10, SNOMED, HCPCS, CPT, and MMSL drug codes (Supplemental Table 7). These indications had to follow a previously qualifying pregnancy code (Supplemental

Table 8) and were allowed inclusion from January 2010 to March 2020. With patients experiencing multiple types (due to multiple pregnancies) only the first was used for analysis. A specific methodology, adapted from previous studies (Hoover et al., 2010; Scholes et al., 2011; Wall--Wieler et al., 2020), was employed for ectopic pregnancy. Ectopic pregnancy was defined by a patient having a qualifying diagnosis code followed over a period of 14 days by either a 1) surgical procedure for treatment 2) medication (of methotrexate) for treatment or 3) a second diagnosis code. Ectopic pregnancy treatment was defined as either surgical, medical, or unknown if neither surgical nor medical were identified. Patients with surgical treatment after medical treatment were classified as surgical. Additionally, cesarean delivery was classified further into planned vs. unplanned/unknown cesarean delivery.

Baseline demographic predictors included the continuous age and year at obstetric outcome, and categorical race/ethnicity (non-Hispanic [NH] American Indian or Alaskan Native [AI/AN], NH-Asian or Pacific Islander [API], NH-Black, Hispanic, NH-White, NH—Other), marital status (married/partner, single), US geographical region based on the one-digit zip code (Northeast, Southeast, Midwest, West), insurance type (private, Medicare, Medicaid, government/miscellaneous, self-pay). An additional baseline clinical predictor consisted of patient comorbidity, with the Charlson Comorbidity Index (CCI) (Charlson et al., 1987). This index is calculated by finding all qualifying health conditions prior to obstetric outcome, weighting them with values according to the methodology, and summing values across each patient to provide a risk of death score. The CCI was also categorized into 0, 1–2, 3–4, and >=5. Codes used to define qualifying conditions for the CCI are displayed in Supplemental Table 9. Final clinical predictors were identified, from previous studies (Brummett et al., 2017; Clarke et al., 2014; Lin et al., 2011; NCQA, 2018; Prabhu et al., 2018; Wall-Wieler et al., 2020), as risk factors of opioid dependence and were identified with ICD-9/10, SNOMED, CPT, NDC, and MMSL codes (Supplemental Table 10a, 10b). These were captured in the two years prior to obstetric outcome, and included pain disorders (arthritis/joint pain, back pain, neck pain/temporomandibular joint disorder [TMJD]/headache, dry eyes, fibromyalgia/chest pain, esophagus pain/irritable bowel syndrome [IBS]/interstitial cystitis, vulvodynia, endometriosis, dyspepsia, sicca syndrome, tinnitus, chronic fatigue syndrome, migraine/insomnia), pelvic inflammatory disease (PID), and prescriptions for psychotropic medications (benzodiazepines and antidepressants). Additionally, any mental disorder (including anxiety, depression, bipolar disorders, post-traumatic stress disorders [PTSD], schizophrenia, eating disorders, disruptive behavior and dissocial disorders, and neurodevelopmental disorders such as autism spectrum disorder and attention deficit hyperactivity disorder [ADHD]), substance use disorder (SUD; including use disorders of alcohol, tobacco, amphetamines, antidepressants, cannabis, cocaine, hallucinogens, inhalants, sedatives, other psychoactives, other stimulants; excluding any OUD indication), and cigarette smoking taking place any time prior to obstetric outcome were included.

2.4. Statistical analysis

Patient demographics and clinical predictors were reported overall as well as stratified by obstetric procedure groups. Means (SDs) and relative frequencies (%'s) were used to display continuous and categorical variables, respectively. Variables were compared between obstetric outcome groups with one-way analysis of variance (ANOVA) for continuous variables, and Chi-square tests for categorical variables. The frequency and risk of OUD were calculated among each obstetric outcome group. Odds ratios (ORs) and 95% confidence intervals (CIs) compared the likelihood of OUD for each obstetric outcome group to normal vaginal delivery. ORs were adjusted for additional demographic and clinical predictors in a logistic regression. CIs were calculated using a profile likelihood and p-values were calculated using a z-statistic. Model goodness-of-fit (GOF) was assessed with the Hosmer-Lemeshow and Stukel test in which insignificant p-values are evidence of sufficient fit. Additional diagnostics were assessed with Pearson and Deviance residuals, and variable multicollinearity was assessed variable inflation factors (VIF; values below 10 indicate less concern for multicollinearity) to ensure independent relationships between predictors and outcome. Predictive ability was assessed with the area under the receiver operating characteristic curve (AUROC; 0.5: poor predictive ability, 1: perfect predictive ability. Due to a large sample size provided by the EHR data, all predictors were of clinical relevance and would be able to be adjusted in the model without having issues of overfitting. Variables, however, were only excluded from modeling if they were deemed to already be captured by a separate variable. For a visual display, model predicted OUD (per 100,000) was plotted against year of obstetric outcome, with different lines drawn for the different obstetric procedure groups.

Two additional analyses looked at 1) the risk of new/persistent opioid prescription and 2) odds of OUD among new/persistent opioid prescribed; while all comparing results between obstetric outcome groups. The first analysis assessed the relative frequency (risk) of new opioid prescription, among those opioid naïve, between obstetric outcome groups as well as the risk of persistent opioid prescription, among those prescribed new opioids, between obstetric outcome groups. Risk ratios (RRs) and 95% CIs compared risk between each obstetric outcome group and normal vaginal delivery. RRs were adjusted for additional demographic and clinical predictors in a modified Poisson regression. The Poisson model makes the distributional assumption of equal mean and variance conditional on predictor variables. To overcome the violation of this assumption, due to the outcome being binary, the Huber-White robust sandwich estimator (Freedman, 2006; Huber, 1967; White, 1982; Zeger and Liang, 1986) was provided to apply robust standard errors. Model GOF was tested on whether the model residual deviance followed a Chi-squared distribution with degrees of freedom (df) equal to the number of observations (n) minus the number of parameters (p) to be estimated (n-p). Variable multicollinearity was also assessed with VIFs.

The second analysis assessed the odds of OUD a) among those not prescribed new opioids b) among those prescribed new opioids and c) among those prescribed persistent opioids; all comparing between obstetric outcome groups in each scenario. ORs and 95% CIs compared odds between each obstetric outcome group and normal vaginal delivery. Adjusted analyses were not applied here.

Final sub-analyses looked into types of ectopic pregnancies (surgical, medical, unknown) and types of cesarean deliveries (planned, unplanned/unknown) with odds of OUD. Additionally, the analysis was repeated while restricting inclusion only until December 31, 2017 to provide a two-year follow-up that ended in December 31, 2019. This was done to compare pre-COVID results to those that included COVID data and see how the results changed. All hypothesis tests were two-sided with a significance level of 5%. All analyses were performed in R version 4.0.2 (R Foundation for Statistical Computing).

2.5. Additional note on string matching for variables identified from medical record codes

For all variables identified from medical record codes of patient EHRs string matching was also employed by searching key terms in the code descriptions. All descriptions were inspected and any that were deemed to not be capturing the variable of interest, were removed.

3. Results

3.1. Descriptive statistics

A total of 632,872 women, initially pregnant, aged 15–44 years old, with no history of OUD, and with no two-year history of opioid prescriptions, were identified for analysis in CRWD. Of these, 65.1% (412,227) had a normal vaginal delivery, 1.8% (11,277) had an ectopic

pregnancy, 17.8% (112,868) had a cesarean delivery, 12.8% (80,806) had a miscarriage, and 2.5% (15,694) had an induced abortion (Table 1). As far as clinical characteristics occurring any time prior to obstetric outcome date, 3.6% had an SUD (not including OUD) and 7.4% had a mental health disorder. Among patients with an ectopic pregnancy, 53.2% were treated surgically, 28.4% were treated medicinally, and 18.5% were unknown. Among patients with a cesarean delivery, 3.4% were known to have a planned c-section, while the rest (96.7%) were either unplanned or unknown. Comparing between obstetric outcome groups, demographic and clinical characteristics all differed significantly (all $P<0.001$) warranting the need for adjusted modeling.

3.2. Inferential statistics

Table 2 shows the crude and adjusted associations of obstetric outcome groups with incidence of OUD over a two-year follow-up. Compared to patients with a normal vaginal delivery, those with an ectopic pregnancy had 84% higher odds of OUD (aOR [95% CI]: 1.84 [1.36, 2.48]), those with a cesarean delivery had 46% higher odds of OUD (aOR [95% CI]: 1.46 [1.29, 1.65]), those with a miscarriage had 119% higher odds of OUD (aOR [95% CI]: 2.19 [1.94, 2.47]), and those with an induced abortion had 131% higher odds of OUD (aOR [95% CI]: 2.31 [1.88, 2.96]). All these associations were significant (all $P<0.001$). Fig. 1 displays the predicted OUD (per 100,000) over years of study, with different lines for the different obstetric outcome groups. Patients with induced abortion and miscarriage had the highest predicted OUD, followed by ectopic pregnancy and c-section, and patients with normal vaginal deliveries had the lowest predicted OUD. The full logistic regression model associations are displayed in Supplemental Table 1.

Among patients who were opioid naïve at obstetric outcome, all other obstetric procedure groups (with the exception of miscarriage) had a higher risk of being prescribed new opioids than those with a normal vaginal delivery. Those with a miscarriage had 27% lower risk of an OUD (aRR [95% CI]: 0.73 [0.72, 0.74]) relative to vaginal delivery. However, among those who were prescribed new opioids, all other obstetric outcome groups had a higher risk of being prescribed persistent opioids than those with a normal vaginal delivery. Those with a miscarriage, ectopic pregnancy, and induced abortion had the highest risk of persistent opioid prescription (aRR [95% CI]: 2.53 [2.10, 3.03], 2.56 [1.87, 3.52], and 2.72 [2.00, 3.71] respectively) relative to vaginal delivery (Table 3). The full modified Poisson regression model associations are displayed in Supplemental Table 2.

Among patients not prescribed new opioids, all other obstetric outcome groups had higher odds of OUD than those with a normal vaginal delivery, however the OR for ectopic pregnancy was not significant (Table 4). With the exception of cesarean delivery, the odds of OUD rose higher for all other obstetric outcome groups when looking among patients prescribed new opioids at obstetric outcome. Other obstetric outcome groups continued to see higher odds of OUD than vaginal delivery patients. Finally, when looking among patients prescribed persistent opioids, the odds of OUD rose even higher for all obstetric outcome groups but due to limited sample sizes, none of these results were significant (Table 4).

3.3. Sub-analyses

Supplemental Table 3 displays the associations of obstetric outcome groups with incidence of OUD, while including also ectopic pregnancy treatment types and cesarean delivery types. All ORs are calculated while comparing to normal vaginal delivery. Across ectopic pregnancy treatment types, those treated surgically and medicinally had the highest OR of OUD. Those with a planned cesarean delivery had a lower OR of OUD than those with an unplanned/unknown cesarean delivery.

The main analysis in Table 2 was repeated by stopping patient inclusion at December 31, 2017 and is displayed in Supplemental Table 4. Patients pre-COVID showed similar results to the main analysis, which included patients during COVID.

4. Discussion

In this retrospective cohort study, we found that in a subset of opioid naïve patients, hospitalizations for ectopic pregnancies, cesarean deliveries, and induced abortions but not miscarriages were associated with an increased risk of receiving new opioid prescriptions at the end of pregnancy. Furthermore, the same obstetric outcomes, including miscarriages, were associated with an increased risk of persistent opioid prescriptions among a subset of patients who had received new opioid prescriptions. When patients were followed for two years to determine odds of OUD, our findings showed that compared to vaginal deliveries, all other obstetric outcomes carried an increased odd of OUD. In particular, the odds ratio of OUD was highest among those who experienced miscarriages and induced abortions. The increased odds of OUD remained in all obstetric outcomes even after stratifying our analysis by patients receiving new, persistent, and not new opioid prescriptions. However, due to limiting sample sizes, significance was diminished in some cases.

Due to the limited number of studies investigating opioid prescription and OUD risk for non-vaginal and non-cesarean obstetric outcomes (e.g., ectopic pregnancy, induced abortion, miscarriage), comparing our results across findings is challenging. However, a study by Wall-Wieler et al. on the association between ectopic pregnancy and persistent opioid use found that nearly half (46%) of opioid naïve patients received new opioid prescriptions after ectopic pregnancy. Additionally, they found that 4% of those who received opioid prescriptions developed persistent opioid use (Wall-Wieler et al., 2020). However, in our data, we found that 43% of opioid naïve ectopic pregnancy patients received new opioid prescriptions, while 0.88% of those who received new opioid prescriptions received persistent prescriptions. One reason for our slightly different results may be the different sources of data. Wall-Weiler et al.'s study utilized a commercial claims database, while ours relied on an EHR database inclusive of all insurance types. EHR data is also limited to prescriptions within a specific healthcare system, while commercial databases capture prescriptions broadly from a variety of healthcare systems. Additionally, our data focused only on opioid prescription rather than filling a prescription. Besides the physical pain associated with an ectopic pregnancy, there is a considerable traumatic aspect involved. This emotional and psychological trauma can have multifaceted effects, potentially playing a role in the observed opioid use patterns.

Furthermore, our adjusted analysis demonstrated an increased risk of new opioid prescriptions among opioid-naive patients who had an ectopic pregnancy, cesarean delivery, and induced abortion compared to those who had a vaginal delivery. In addition, regardless of the obstetric outcome, all those who had already received new opioid prescriptions were more likely to develop persistent use than those who had a vaginal delivery. These results confirm other findings suggesting that receiving a prior opioid prescription during the postpartum period is a risk factor for prolonged use (Peahl et al., 2019). Of note, except for miscarriages, all other obstetric outcomes examined among opioid-naive patients were associated with an increased risk of new opioid prescription, suggesting that for many women of reproductive age, pain management for cesarean delivery, ectopic pregnancy, or induced abortions may be their first exposure to prescription opioids. Therefore, exposure to these obstetric outcomes can be regarded as a potential gateway to persistent opioid use. This has been confirmed in other studies (Gibbs et al., 2021; Peahl et al., 2019; Sun et al., 2016; Wall-Wieler et al., 2020) and has important clinical implications, particularly for cesarean section deliveries, given that a substantial proportion of deliveries in the United States occur via cesarean sections (Osterman et al., 2022). On the contrary, experiencing a miscarriage was protective against new opioid prescriptions. We suspect that this is because a substantial proportion of miscarriages occur during the first trimester (Dugas and Slane, 2022;

Table 1
Baseline characteristics of women 15–44 years old with either first normal vaginal delivery, ectopic pregnancy, cesarean delivery, miscarriage, induced abortion (from January 1, 2010 to March 31, 2020) in Cerner-affiliated health systems, with no prior diagnosis of opioid use disorder (OUD) or OUD up to one month post diagnosis, and no opioid prescription from 2 years to 8 days before pregnancy end date (opioid naïve).

	Total	Normal vaginal delivery	Ectopic pregnancy	Cesarean delivery	Miscarriage	Induced abortion	p-value[11]
	n (%[1])	n (%[1])	n (%[1])	n (%[1])	n (%[1])	n (%[1])	
Total	632,872	412,227 (65.1[2])	11,277 (1.8[2])	112,868 (17.8[2])	80,806 (12.8[2])	15,694 (2.5[2])	
Demographic							
Age (Years)[3]	27.97 (6.08)	27.45 (5.87)	29.42 (5.91)	29.02 (5.98)	28.91 (6.75)	28.13 (6.88)	<0.001[12]
Year at obstetric outcome							<0.001
2010	7879 (1.2)	4434 (1.1)	138 (1.2)	1277 (1.1)	1525 (1.9)	505 (3.2)	
2011	31,632 (5.0)	22,680 (5.5)	311 (2.8)	4007 (3.6)	3429 (4.2)	1205 (7.7)	
2012	58,605 (9.3)	41,940 (10.2)	678 (6.0)	7866 (7.0)	5725 (7.1)	2396 (15.3)	
2013	66,294 (10.5)	45,432 (11.0)	776 (6.9)	10,342 (9.2)	6443 (8.0)	3301 (21.0)	
2014	75,494 (11.9)	48,824 (11.8)	984 (8.7)	14,195 (12.6)	7703 (9.5)	3788 (24.1)	
2015	70,622 (11.2)	41,990 (10.2)	1181 (10.5)	16,233 (14.4)	8328 (10.3)	2890 (18.4)	
2016	65,127 (10.3)	41,910 (10.2)	1470 (13.0)	11,856 (10.5)	9552 (11.8)	339 (2.2)	
2017	74,648 (11.8)	47,480 (11.5)	1718 (15.2)	14,347 (12.7)	10,753 (13.3)	350 (2.2)	
2018	80,422 (12.7)	51,574 (12.5)	1780 (15.8)	14,543 (12.9)	12,113 (15.0)	412 (2.6)	
2019	82,284 (13.0)	53,331 (12.9)	1786 (15.8)	14,603 (12.9)	12,153 (15.0)	411 (2.6)	
2020	19,865 (3.1)	12,632 (3.1)	455 (4.0)	3599 (3.2)	3082 (3.8)	97 (0.6)	
Race							<0.001
NH-AI/AN[4]	7940 (1.3)	5609 (1.4)	63 (0.6)	1414 (1.3)	746 (0.9)	108 (0.7)	
NH-API[5]	28,083 (4.4)	18,750 (4.5)	506 (4.5)	5357 (4.7)	2891 (3.6)	579 (3.7)	
NH-Black	72,181 (11.4)	42,071 (10.2)	2250 (20.0)	13,586 (12.0)	11,713 (14.5)	2561 (16.3)	
Hispanic/Latino	168,029 (26.6)	112,195 (27.2)	2580 (22.9)	27,394 (24.3)	21,063 (26.1)	4797 (30.6)	
NH—Other	31,170 (4.9)	19,367 (4.7)	609 (5.4)	5237 (4.6)	4780 (5.9)	1177 (7.5)	
NH-White	325,469 (51.4)	214,235 (52.0)	5269 (46.7)	59,880 (53.1)	39,613 (49.0)	6472 (41.2)	
Marital status							<0.001
Single	300,060 (47.4)	191,033 (46.3)	6499 (57.6)	50,457 (44.7)	42,663 (52.8)	9408 (59.9)	
Married/Partner	332,812 (52.6)	221,194 (53.7)	4778 (42.4)	62,411 (55.3)	38,143 (47.2)	6286 (40.1)	
US region							<0.001
Northeast	153,483 (24.3)	92,006 (22.3)	3889 (34.5)	26,922 (23.9)	24,164 (29.9)	6502 (41.4)	
Southeast	68,256 (10.8)	41,305 (10.0)	1722 (15.3)	13,367 (11.8)	10,741 (13.3)	1121 (7.1)	
Midwest	181,106 (28.6)	116,634 (28.3)	2528 (22.4)	36,802 (32.6)	22,637 (28.0)	2505 (16.0)	
West	230,027 (36.3)	162,282 (39.4)	3138 (27.8)	35,777 (31.7)	23,264 (28.8)	5566 (35.5)	
Insurance							<0.001
Private	292,422 (46.2)	189,255 (45.9)	5202 (46.1)	56,414 (50.0)	35,938 (44.5)	5613 (35.8)	
Medicare	3129 (0.5)	1587 (0.4)	73 (0.6)	790 (0.7)	548 (0.7)	131 (0.8)	
Medicaid	254,304 (40.2)	170,948 (41.5)	3958 (35.1)	41,622 (36.9)	30,908 (38.2)	6868 (43.8)	
Govt/Misc	25,076 (4.0)	16,430 (4.0)	445 (3.9)	4003 (3.5)	3638 (4.5)	560 (3.6)	
Self-Pay	57,941 (9.2)	34,007 (8.2)	1599 (14.2)	10,039 (8.9)	9774 (12.1)	2522 (16.1)	
Charlson comorbidity index (CCI)							<0.001
0	595,742 (94.1)	389,889 (94.6)	10,752 (95.3)	104,411 (92.5)	75,563 (93.5)	15,127 (96.4)	
1–2	24,934 (3.9)	15,021 (3.6)	323 (2.9)	5758 (5.1)	3343 (4.1)	489 (3.1)	

(continued on next page)

Table 1 (*continued*)

	Total	Normal vaginal delivery	Ectopic pregnancy	Cesarean delivery	Miscarriage	Induced abortion	p-value[11]
	n (%[1])	n (%[1])	n (%[1])	n (%[1])	n (%[1])	n (%[1])	
Total	632,872	412,227 (65.1[2])	11,277 (1.8[2])	112,868 (17.8[2])	80,806 (12.8[2])	15,694 (2.5[2])	
3–4	11,648 (1.8)	7082 (1.7)	190 (1.7)	2529 (2.2)	1785 (2.2)	62 (0.4)	
>=5	548 (0.1)	235 (0.1)	12 (0.1)	170 (0.2)	115 (0.1)	16 (0.1)	
Clinical variables present in two years before pregnancy end date (except where noted)							
Arthritis/Joint Pain	27,358 (4.3)	16,571 (4.0)	525 (4.7)	5286 (4.7)	4564 (5.6)	412 (2.6)	<0.001
Back Pain	14,499 (2.3)	9960 (2.4)	173 (1.5)	2572 (2.3)	1422 (1.8)	372 (2.4)	<0.001
Neck pain, TMJD[6], headache, dry eyes	29,921 (4.7)	19,913 (4.8)	471 (4.2)	5157 (4.6)	3943 (4.9)	437 (2.8)	<0.001
Fibromyalgia, chest pain, esophagus pain, IBS[7], interstitial cystitis, vulvodynia, endometriosis, dyspepsia, sicca syndrome, tinnitus, chronic fatigue syndrome	17,030 (2.7)	10,518 (2.6)	307 (2.7)	3191 (2.8)	2765 (3.4)	249 (1.6)	<0.001
Migraine, insomnia	9697 (1.5)	5996 (1.5)	156 (1.4)	1879 (1.7)	1532 (1.9)	134 (0.9)	<0.001
Substance use disorder[8,9]	22,850 (3.6)	13,817 (3.4)	535 (4.7)	4401 (3.9)	3652 (4.5)	445 (2.8)	<0.001
Mental health disorder[8]	46,918 (7.4)	28,707 (7.0)	782 (6.9)	9254 (8.2)	7433 (9.2)	742 (4.7)	<0.001
Cigarette smoking[8]	27,624 (4.4)	18,614 (4.5)	484 (4.3)	4754 (4.2)	3382 (4.2)	390 (2.5)	<0.001
Pelvic inflammatory disease	19,400 (3.1)	12,181 (3.0)	333 (3.0)	3421 (3.0)	3111 (3.8)	354 (2.3)	<0.001
Benzodiazepine prescription	26,137 (4.1)	15,176 (3.7)	548 (4.9)	5557 (4.9)	4099 (5.1)	757 (4.8)	<0.001
Antidepressant prescription	12,276 (1.9)	7177 (1.7)	172 (1.5)	2800 (2.5)	1951 (2.4)	176 (1.1)	<0.001
Type of Ectopic Treatment[10]							
Surgical	–	–	5996 (53.2)	–	–	–	
Medical	–	–	3200 (28.4)	–	–	–	
Unknown	–	–	2081 (18.5)	–	–	–	
Type of cesarean delivery							
Planned	–	–	–	3783 (3.4)	–	–	
Unplanned/Unknown	–	–	–	109,085 (96.7)	–	–	

[1] Column %'s;.
[2] % out of total (632,872);
[3] mean (standard deviation);
[4] American Indian or Alaskan Native;
[5] Asian or Pacific Islander;
[6] temporomandibular joint disorder;
[7] irritable bowel syndrome;
[8] ever occurring prior to pregnancy end date;
[9] excluding opioid use disorder.
[10] out of only those with ectopic pregnancy;
[11] Chi-square test (unless otherwise noted);
[12] One-way ANOVA.

Table 2
Associations of pregnancy end groups with incidence of OUD (two-year follow-up).

Groups	n (risk[1])	OR[2] (95% CI)	a[3]OR[2] (95% CI)	p
Normal vaginal delivery	904 (219.30)	1 [Reference]	1 [Reference]	–
Ectopic pregnancy	46 (407.91)	1.86 (1.38, 2.51)	1.84 (1.36, 2.48)	<0.001
Cesarean delivery	368 (326.04)	1.49 (1.32, 1.68)	1.46 (1.29, 1.65)	<0.001
Miscarriage	411 (508.63)	2.33 (2.07, 2.61)	2.19 (1.94, 2.47)	<0.001
Induced abortion	71 (452.40)	2.07 (1.62, 2.63)	2.31 (1.80, 2.96)	<0.001

[1] Per 100,000 individuals;
[2] Odds of OUD for given group, compared to normal vaginal delivery;
[3] Adjusted for all variables shown in Supplemental Table 1.

Wilcox et al., 1988; Zinaman et al., 1996), and therefore may not require intensive pain management. Additionally, several first-trimester miscarriages may be managed at home with over-the-counter pain medications or other pain management techniques (Walter and Alvarado, 2018).

Our findings regarding the odds of OUD showed that all obstetric outcomes were associated with a heightened risk of OUD diagnosis compared to those with a vaginal delivery. Those with miscarriages and induced abortions had the highest risk of developing OUDs, relative to those with vaginal deliveries, and the risks were higher among those newly prescribed opioids. Furthermore, prior research has demonstrated that those who experience miscarriages and induced abortions also experience intense grief, trauma, psychological distress, and even clinically recognizable depression and anxiety following their losses (Bellieni and Buonocore, 2013; deMontigny et al., 2017; Hutti et al., 2015; Kulathilaka et al., 2016). Additionally, while some individuals who undergo induced abortions may encounter stigma and feelings of isolation (Astbury-Ward et al., 2012), it is equally important to

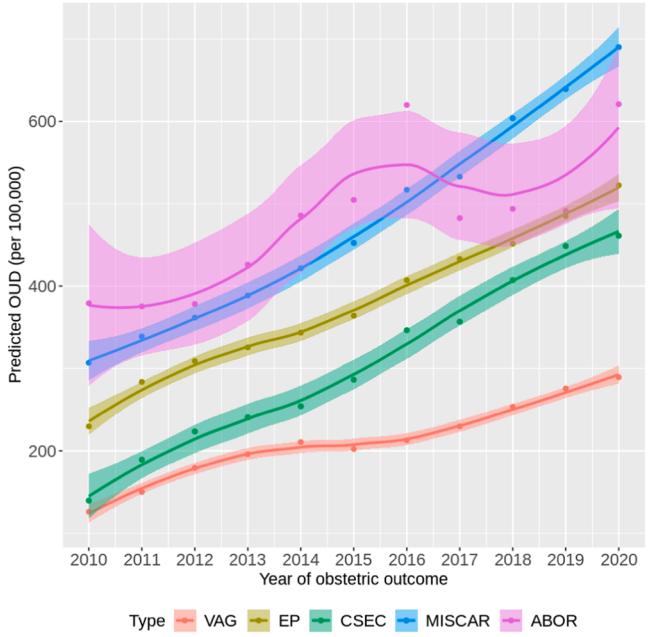

Fig. 1. Predicted OUD vs. year of diagnosis (by obstetric outcome).

recognize that many experience relief following the procedure. The diverse emotional responses to induced abortion highlight the complexity of individual experiences. These mental states often correlate with an increased risk of substance use disorders (Bellieni and Buonocore, 2013; Sullins, 2019) and therefore, may partly explain our findings. Moreover, the challenges and mental health outcomes of continuing an unwanted pregnancy should not be overlooked. Additional research is needed to understand better the role of miscarriages and induced abortions in OUD risk.

The results of our study have multiple clinical implications. Approaches to pain management by clinicians for obstetric procedures and, perhaps importantly, pain management for miscarriages and abortions should consider the potential for future chronic use. In addition, while routine 3-week postpartum visits are now advocated by ACOG, it is worth noting that many patients undergoing induced abortions often lack comprehensive follow-up care. This limited care might be attributed to the segregation of abortion clinics from other women's health and primary care centers. Given the potential risk of persistent opioid use and OUD, there is an urgent need for standardized and thorough follow-up after induced abortions, moving beyond mere phone check-ins to more substantive consultations.

There are important limitations in our research that warrant discussion. We used different obstetric outcomes as our predictor of interest with the same inclusion/exclusion criteria used in relation to any of predictor groups. However, the time preceding an ectopic pregnancy or miscarriage could be vastly different than the time preceding a normal vaginal delivery or a c-section. Pain management, as captured with opioid prescription, would vary across the different groups due to the presence or absence of a viable fetus. We extended our look-back window up to two years so that we could still capture women having an opioid prescription history before prescriptions would be halted due to a viable pregnancy. However, there are still differences in prior opioid prescribing due to the various obstetric outcome groups, and this remains a limitation. As there is no standard definition for persistent opioid use, we based our definition on prior research (Brummett et al., 2017; Peahl et al., 2019; Wall-Wieler et al., 2020) and acknowledge that our estimates may differ based on how persistent opioid use is defined. Moreover, the data we present on new opioid and persistent use are based solely on provider prescription patterns as recorded in pharmacy and claims data, therefore, we have no way of knowing actual opioid use patterns by patients. We calculated risk of OUD stratified by new/-persistent opioid prescription and due to the limited sample size of rare outcomes among rare stratification groups, results are limited in their high variability. It is also important to consider the complex interactions between prescribed and illicit opioids. For some individuals, an initial exposure to prescription opioids might be followed by a transition to illicit substances, potentially confounding the direct link between obstetric outcomes and OUD. Our data, by capturing OUD diagnoses, tries to address this broader spectrum but might not capture the nuanced transitions between different types of opioids.

We relied on routine billing codes which may be subject to coding errors and misclassification. Misclassification may also be present on patients who were undiagnosed or received diagnoses/prescriptions

Table 3
Associations of pregnancy end groups with new/persistent opioid prescriptions.

	New opioid prescriptions among opioid naïve patients				Persistent opioid prescriptions among new opioid prescribed patients			
Groups	n (risk[1])	RR[2] (95% CI)	a[4]RR[2] (95% CI)	p	n (risk[1])	RR[3] (95% CI)	a[4]RR[3] (95% CI)	p
Normal vaginal delivery	111,716 (271.01)	1 [Reference]	1 [Reference]	–	428 (3.83)	1 [Reference]	1 [Reference]	–
Ectopic pregnancy	4850 (430.08)	1.59 (1.55, 1.62)	1.45 (1.42, 1.48)	<0.001	43 (8.87)	2.31 (1.69, 3.16)	2.56 (1.87, 3.52)	<0.001
Cesarean delivery	47,544 (421.24)	1.55 (1.54, 1.57)	1.49 (1.48, 1.50)	<0.001	246 (5.17)	1.35 (1.15, 1.58)	1.42 (1.21, 1.66)	<0.001
Miscarriage	17,307 (214.18)	0.79 (0.78, 0.80)	0.73 (0.72, 0.74)	<0.001	166 (9.59)	2.50 (2.09, 2.99)	2.53 (2.10, 3.03)	<0.001
Induced abortion	4146 (264.18)	0.97 (0.95, 1.00)	1.09 (1.06, 1.12)	<0.001	46 (11.10)	2.90 (2.14, 3.92)	2.72 (2.00, 3.71)	<0.001

[1] Per 1000 individuals;
[2] Risk of new opioid prescription for given group, compared to normal vaginal delivery;
[3] Risk of persistent opioid prescription for given group, compared to normal vaginal delivery;
[4] Adjusted for all variables shown in Supplemental Table 2.

Table 4
Associations of pregnancy end groups and new/persistent opioid prescriptions with OUD (two-year follow-up).

	OUD among not newly prescribed opioid patients		OUD among newly prescribed opioid patients		OUD among persistently prescribed opioid patients	
Groups	n (risk[1])	OR[2] (95% CI)	n (risk[1])	OR[2] (95% CI)	n (risk[1])	OR[2] (95% CI)
Normal vaginal delivery	629 (209.31)	1 [Reference]	275 (246.16)	1 [Reference]	8 (1869.16)	1 [Reference]
Ectopic pregnancy	19 (295.63)	1.41 (0.90, 2.23)	27 (556.70)	2.27 (1.53, 3.37)	2 (4651.16)	2.56 (0.53, 12.46)
Cesarean delivery	230 (352.09)	1.68 (1.45, 1.96)	138 (290.26)	1.18 (0.96, 1.45)	11 (4471.54)	2.46 (0.97, 6.19)
Miscarriage	311 (489.77)	2.35 (2.05, 2.69)	100 (577.80)	2.36 (1.87, 2.96)	5 (3012.05)	1.63 (0.53, 5.06)
Induced abortion	45 (389.68)	1.87 (1.38, 2.53)	26 (627.11)	2.56 (1.71, 3.83)	3 (6521.74)	3.66 (0.94, 14.32)

[1] Per 100,000 individuals;
[2] Odds of OUD for given group, compared to normal vaginal delivery.

outside of Cerner health systems. Further, a notable limitation is the challenge of differentiating disorders stemming from prescription versus illicit opioids under OUD diagnoses. While our study offers a holistic view, the interplay between these categories and their specific impacts on obstetric outcomes could introduce confounding elements that we might not have entirely accounted for. We did account for possible delays in prior OUD conditions extending into the hospital stay or after, by designating a 30-window after hospitalization in which we excluded all OUD diagnoses.

Additionally, approximately 3% of our sample receiving a c-section were defined as "planned" however many of the diagnosis codes for c-section did not designate between planned or unplanned, and analyses combined unknown designations with unplanned designations. Thus, a large amount of heterogeneity remained in the "unplanned/unknown" group with presumably many planned c-section patients erroneously remaining in that group. It is also worth considering external factors that might influence the patterns observed. For instance, individuals with OUD might have a higher risk of unintended pregnancies. Despite these limitations, our use of an extensive national database that allows us to effectively investigate the associations between several obstetric outcomes, opioid prescribing patterns, and OUD strengthens our study.

5. Conclusion

In summary, our study has demonstrated an increased risk of persistent opioid use and OUD following a cesarean section, ectopic pregnancy, miscarriage, or induced abortion compared to normal vaginal delivery. In doing so, our findings contribute to the sparse literature on the link between specific obstetric outcomes, notably miscarriage and induced abortions, and opioid use patterns in a maternal population. Our findings should inform clinical decision-making and support the need for physician education and the widespread adoption of evidence-based clinical guidelines for safe and effective pain management. Given the demonstrated association between certain obstetric procedures and subsequent opioid use or OUD, it is imperative for clinicians to exercise caution when prescribing opioids, especially for procedures that result in patients being discharged home with these medications. It is paramount to carefully evaluate the necessity and duration of opioid use in such instances.

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Fares Qeadan: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Benjamin Tingey:** Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – review & editing. **Nana Akofua Mensah:** Investigation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

No conflict declared.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dadr.2023.100210.

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