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Opioid Prescribing After Childbirth and Risk for Serious Opioid-Related Events: A Cohort Study

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Background:

Although persistent opioid use after surgery, including cesarean birth, has been described, the risk for overdose and other serious opioid-related events (SOREs) after childbirth, specifically vaginal birth, remains unclear (1, 2).

Corresponding Author: Sarah S. Osmundson, MD, MS, 1161 21st Avenue, South B1118 MCN, Nashville, TN 37232; sarah.osmundson@vumc.org. **Reproducible Research Statement:** *Study protocol and statistical code:* Available from Dr. Osmundson (sarah.osmundson@vumc.org). *Data set:* Not available.
Note: Dr. Osmundson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Objective:

To assess risk for SOREs associated with postpartum opioid prescribing after childbirth, including both vaginal and cesarean births.

Methods and Findings:

We studied women aged 15 to 44 years enrolled in Tennessee Medicaid (TennCare) who were discharged after childbirth between 1 January 2007 and 20 August 2014. TennCare data were supplemented with birth certificate information and hospital discharge data from the Tennessee Hospital Discharge Data System. This study was approved by the institutional review boards of Vanderbilt University Medical Center and the Tennessee Department of Health and by the Division of TennCare.

We included women enrolled in TennCare from 180 days before birth through 41 days after hospital discharge who had no history of at least opioid prescription or opioid use disorder 180 days through 3 days before birth (baseline/antepartum period). The study exposure was the number of opioid prescriptions filled (1, 2, or ≥3) during the postpartum period (3 days before birth to 41 days after hospital discharge). Follow-up began on postdischarge day 42 and continued through the earliest of 365 days of follow-up, loss of enrollment, death, or achievement of our SORE outcome (a composite of persistent opioid use, opioid use disorder diagnosis, buprenorphine or methadone prescription fill, opioid overdose diagnosis, or opioid-related death). Persistent opioid use was defined as filling greater than a 90-day supply of opioids within a 180-day window during follow-up (excluding the postpartum exposure prescriptions), with no gaps in supply greater than 30 days.

We used adjusted Cox regression models stratified by birth type to examine the relationship between postpartum opioid prescription exposure and time to SORE, with adjustment for study covariates that could confound the relationship (Table). Multiple imputation addressed missing covariate values (<4% of total observations). We obtained separate estimates for birth type by including an interaction term in the regression model. Because a woman could contribute more than 1 birth in our analyses, we also accounted for the resulting lack of independence using the Huber-White variance estimation and calculated robust SEs for our model estimates. Analyses were performed using Stata, version 15.1 (StataCorp).

Among 209 215 births to 161 318 women (69.2% vaginal births and 30.8% cesarean births) that met inclusion criteria, 59% of vaginal births and 91% of cesarean births involved filling of 1 or more opioid prescriptions; 10.5% and 24.4%, respectively, involved filling of a second postpartum opioid prescription. We identified SOREs in 4582 women (27.2 per 1000 person-years) (persistent opioid use [69.1%], substance use disorder diagnosis [18.5%], buprenorphine or methadone prescription fill [10.1%], opioid overdose [2.1%], and opioid-related death [0.2%]).

The covariate-adjusted SORE rate increased with increasing number of postpartum opioid prescriptions (Figure). Similar patterns were demonstrated in the analysis by birth route (*P* for interaction = 0.173). Our findings were robust to the multiple sensitivity analyses performed (Table).

Discussion:

We found that compared with not filling prescriptions, filling opioid prescriptions in the postpartum period was strongly associated with increased risk for SOREs during the subsequent year in a prescription frequency–dependent manner. This association was consistently observed regardless of birth route. In addition, our study highlights the high frequency of vaginal births affected by opioid prescribing in our state.

Although prior literature has described persistent opioid use after cesarean birth, knowledge of risks associated with opioid prescribing after vaginal birth is limited (3). This study integrated birth certificate data with claims and hospital registry information and was designed to augment information from studies that focused exclusively on persistent opioid use. Our data indicate that opioid prescribing after vaginal birth was common in our study, involving 59% of vaginal births, and imparts a significant and equally important risk for SOREs compared with cesarean birth. Current clinical guidelines do not provide specific recommendations for opioid prescribing after childbirth (4). Design and implementation of rational opioid prescribing guidelines would be an opportunity to reduce this risk.

Our study had limitations. We utilized Medicaid prescription data to estimate opioid use from a single state heavily affected by the opioid epidemic; we lacked information on actual opioid use, including illicit use. Nevertheless, almost half of all births in the United States are covered by Medicaid (5), so studies characterizing opioid risks in this vulnerable population are important. We cannot rule out the possibility that we included some women with undisclosed opioid use disorders who stopped use during pregnancy and resumed after birth, although a sensitivity analysis restricted to women with a complete year of data before birth yielded results consistent with those of our primary analysis. Although substantially attenuated, the risk for SOREs remained strongly and consistently associated with postpartum opioid prescribing when we examined only the most severe SORE outcomes.

In summary, women receiving postpartum prescription opioids have increased risk for SOREs that is related to prescription frequency, regardless of birth route. Reducing opioid prescribing after vaginal birth and in the postpartum period in general may improve outcomes for postpartum women.

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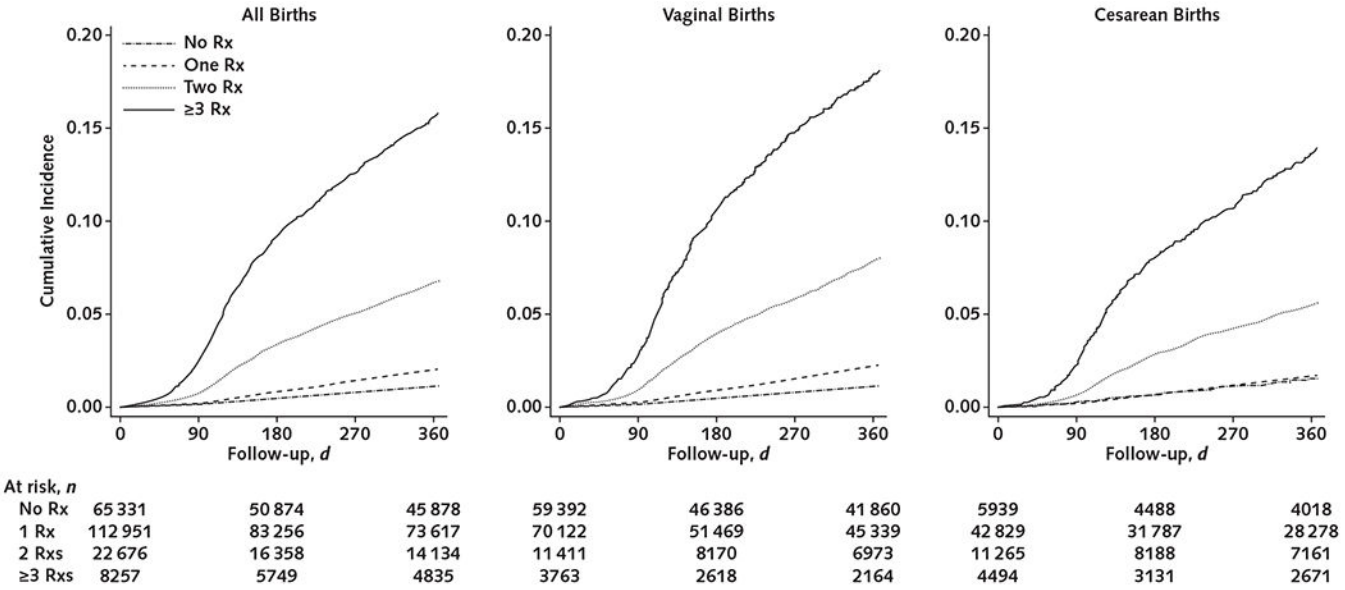

At risk, *n*									
No Rx	65 331	50 874	45 878	59 392	46 386	41 860	5939	4488	4018
1 Rx	112 951	83 256	73 617	70 122	51 469	45 339	42 829	31 787	28 278
2 Rxs	22 676	16 358	14 134	11 411	8170	6973	11 265	8188	7161
≥3 Rxs	8257	5749	4835	3763	2618	2164	4494	3131	2671

Figure.

Adjusted cumulative incidence of serious opioid-related events.

Rx = prescription.

Table.

Risk for SOREs, by Number of Postpartum Prescriptions and Stratified by Delivery Type

Outcome, by Delivery Type	No Prescription	1 Prescription	2 Prescriptions	≥3 Prescriptions
All births, *n* (%)	65 331 (31.2)	112 951 (54.0)	22 676 (10.8)	8257 (4.0)
SORE, *n*	613	1780	1182	1007
Rate per 1000 PYs (95% CI)	11.3 (10.5–12.3)	19.7 (18.8–20.7)	66.5 (62.8–70.3)	160.0 (150.4–170.2)
Adjusted HR (95% CI)*	Reference	1.4 (1.3–1.6)	3.6 (3.2–4.0)	7.0 (6.3–7.9)
SORE (excluding persistent opioid prescriptions), *n*	289	671	278	178
Rate per 1000 PYs (95% CI)	5.3 (4.8–6.0)	7.4 (6.9–8.0)	15.6 (13.9–17.6)	28.3 (24.4–32.8)
Adjusted HR (95% CI)*	Reference	1.1 (0.9–1.3)	1.6 (1.3–2.0)	2.7 (2.1–3.4)
Vaginal births, *n (%)*	59 392 (41.1)	70 122 (48.5)	11 411 (7.9)	3763 (2.6)
SORE, *n*	540	1217	694	522
Rate per 1000 PYs (95% CI)	11.0 (10.1–11.9)	21.8 (20.6–23.1)	78.1 (72.5–84.1)	181.7 (167.1–197.6)
Adjusted HR (95% CI)	Reference	1.5 (1.3–1.7)	3.7 (3.3–4.2)	7.2 (6.3–8.2)
SORE (excluding persistent opioid prescriptions), *n*	246	455	164	98
Rate per 1000 PYs (95% CI)	5.0 (4.4–5.7)	8.1 (7.4–8.9)	18.4 (15.8–21.5)	34.4 (28.2–41.9)
Adjusted HR (95% CI)*	Reference	1.1 (0.9–1.3)	1.8 (1.5–2.2)	2.9 (2.3–3.8)
Cesarean births, *n (%)*	5939 (9.2)	42 829 (66.4)	11 265 (17.5)	4494 (7.0)
SORE, *n*	73	563	488	485
Rate per 1000 PYs (95% CI)	15.2 (12.1–19.1)	16.4 (15.1–17.8)	54.8 (50.2–59.9)	140.9 (128.9–154.0)
Adjusted HR (95% CI)	Reference	1.2 (0.9–1.5)	2.9 (2.2–3.6)	5.9 (4.6–7.6)
SORE (excluding persistent opioid prescriptions), *n*	43	216	114	80
Rate per 1000 PYs (95% CI)	8.9 (6.6–12.0)	6.3 (5.5–7.2)	12.8 (10.7–15.4)	23.2 (18.7–28.9)
Adjusted HR (95% CI)*	Reference	0.7 (0.5–1.0)	1.0 (0.7–1.4)	1.5 (1.03–2.5)
Sensitivity analyses (all births)†				
Including nonopioid deaths in outcome	Reference	1.4 (1.2–1.6)	3.5 (3.2–3.9)	6.9 (6.2–7.7)
Excluding women who filled single opioid prescription during pregnancy	Reference	1.5 (1.3–1.7)	3.7 (3.3–4.2)	7.6 (6.7–8.7)
Excluding complicated births	Reference	1.6 (1.4–1.8)	3.8 (3.4–4.4)	8.0 (7.0–9.2)
Excluding women without enrollment for 1 y before birth	Reference	1.5 (1.3–1.8)	3.1 (2.6–3.7)	6.1 (5.0–7.4)

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HR = hazard ratio; PY = person-year; SORE = serious opioid-related event.

*Adjusted estimates were obtained from Cox regression models that adjusted for age, parity, income, distance to the birth hospital, race, ethnicity, tobacco use, rurality, Tennessee region, delivery year, severe maternal morbidity, perineal lacerations, bilateral tubal ligation, filling 1 opioid prescription during pregnancy, and conditions precluding nonsteroidal anti-inflammatory drug use (e.g., chronic kidney disease). Models also adjusted for mental health medications, mental health conditions, pain-related diagnoses, and procedures; these conditions were measured during both the antepartum and postpartum periods. To impute missing data for age, parity, income, and distance to the birth hospital, we used multiple imputation by chained equations and 10 imputed data sets (mi impute command in Stata). We assessed the fulfillment of the proportional hazards assumption through examination of Schoenfeld residuals and log-log plots.

†Five sensitivity analyses were performed for the following scenarios: including 91 nonopioid deaths in the composite outcome, excluding 3166 women with persistent opioid use from the primary outcome, excluding women who filled a single opioid prescription during pregnancy (total n = 180 959), excluding complicated births (n = 165 640), and excluding women without enrollment for 1 year before birth (n = 103 335). The data presented are HRs and 95% CIs.