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Prescription Opioid Dose After Vaginal Delivery and the Risk of Serious Opioid-Related Events: A Retrospective Cohort Study

Andrew D. Wiese, PhD, MPH [a,*], Sarah S. Osmundson, MD, MPH [b], Edward Mitchel Jr., MS [a], Margaret Adgent, PhD, MSPH [a], Sharon Phillips, MSPH [c], Stephen W. Patrick, MD, MPH, MS [a,d,e], Arlyn Horn, PharmD, MPH [a,†], Lauren R. Samuels, PhD [c], Marie R. Griffin, MD, MPH [a], Carlos G. Grijalva, MD, MPH [a,f]

[a] *Department of Health Policy, Vanderbilt University Medical Center, Nashville, Tennessee*
[b] *Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, Tennessee*
[c] *Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee*
[d] *Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee*
[e] *Vanderbilt Center for Child Health Policy, Vanderbilt University Medical Center, Nashville, Tennessee*
[f] *Mid-South Geriatric Research Education and Clinical Center, VA Tennessee Valley Health Care System, Nashville, Tennessee*

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A B S T R A C T

Purpose: Postpartum opioid use remains common among women with uncomplicated vaginal delivery and may increase the risk of serious opioid-related events. Therefore, we examined the association between the dose of the first filled opioid prescription after vaginal delivery and the subsequent risk of serious opioid-related events.
Methods: We conducted a retrospective cohort study among women enrolled in Tennessee Medicaid with a vaginal delivery (2007–2015). We used Cox proportional hazards regression to model adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for serious opioid-related events after delivery according to the dose (morphine milligram equivalents [MME]) of the first postpartum opioid prescription, accounting for comorbidities, medication use, parity, and delivery complications. Serious opioid-related events were defined as the occurrence of persistent opioid use, a methadone or buprenorphine fill, opioid use disorder diagnosis, opioid overdose, or opioid-related death. We used filled pharmacy data to characterize the dose of the first postpartum opioid prescription filled within 4 days after delivery.
Results: More than one-half of women (53.2%; $n = 147{,}598$) filled an opioid prescription within 4 days of a vaginal delivery. After accounting for baseline risk factors, filling a postpartum opioid prescription was associated with an increased risk of serious opioid-related events across all dose categories, compared with women filling none (aHR 1–99 MME, 1.52; 95% CI, 1.33–1.74; aHR 100-149 MME, 1.41; 95% CI, 1.26–1.58; aHR 150–199 MME, 1.40; 95% CI, 1.26–1.57: and aHR $\geq$200 MME, 1.60; 95% CI, 1.43–1.78).
Conclusions: Filling a postpartum opioid prescription after a vaginal delivery was associated with an increased risk of serious opioid-related events, regardless of dose. Prescribing guidelines should discourage the routine prescribing of opioids after vaginal delivery.

Among U.S. women, opioid prescribing is ubiquitous among opioid-naïve women after cesarean delivery but also remains common after uncomplicated vaginal delivery (Jarlenski et al., 2017; Prabhu et al., 2018). For many women undergoing vaginal delivery, postpartum opioid use is their first exposure to prescribed opioids (Badreldin, Grobman, & Yee, 2018; Komatsu, Carvalho, & Flood, 2017). Postpartum opioid use is associated with an increased risk of developing persistent opioid use (Bateman et al., 2016; Osmundson et al., 2020; Osmundson et al., 2019; Peahl et al., 2019). Recent evidence suggests that both the total opioid dose and number of opioid prescriptions filled in the

* Correspondence to: Andrew D. Wiese, PhD, MPH, Department of Health Policy, Vanderbilt University Medical Center, Suite 2600, Village at Vanderbilt, 1500 21st Ave South, Nashville, TN 37212. Phone: (615) 875-7997; fax: (615) 322-2610.
E-mail address: andrew.d.wiese.1@vumc.org (A.D. Wiese).
† Author deceased.

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initial 6-week postpartum period are also strongly associated with an increased risk of more severe opioid-related events (i.e., opioid use disorder, opioid-related overdose, and opioid-related death), regardless of delivery route (Osmundson et al., 2020; Peahl et al., 2019).

Although prescribing guidelines in the general population consider that certain dose thresholds are associated with higher risks of serious opioid-related events, whether certain opioid doses are associated with a higher risk of serious-opioid related events among women prescribed opioids after vaginal delivery remains unclear (Dowell, Haegerich, & Chou, 2016). This remains an important unanswered question because the prescribing rates after vaginal delivery vary markedly by country, region, and hospital, suggesting that postpartum opioid prescribing decisions are influenced by factors other than patient need, including provider preference and nonclinical patient factors (maternal age, race/ethnicity, insurance provider, rurality of residence, and distance to hospital) (Badreldin, Grobman, & Yee, 2019; Becker, Gibbins, Perrone, & Maughan, 2018; Komatsu et al., 2017; Osmundson et al., 2019; Schmidt, Berger, Day, & Swenson, 2018; Wong & Girard, 2018). Therefore, we sought to test the hypothesis that among pregnant women who had a vaginal delivery, the risk of serious opioid-related events differed by the dose of their first postpartum opioid prescription.

Methods

Data Sources

We conducted a retrospective cohort study of women enrolled in Tennessee Medicaid (TennCare). TennCare, the managed care Medicaid program in Tennessee, provides insurance for more than 50% of the annual births in Tennessee. TennCare data include information on enrollment, demographics, health care encounters, comorbidities, and prescription fills. We supplemented TennCare data with information from Tennessee birth and death certificates, and the Tennessee Hospital Discharge Data System, a registry of all hospital-based encounters in Tennessee (Osmundson et al., 2019; Ray, Chung, Murray, Hall, & Stein, 2016). This study was approved by the institutional review board.

Study Cohort and Follow-Up

We identified women aged 15–44 years enrolled in TennCare with a vaginal delivery of a live infant from January 2007 through September 2014 (follow-up through September 2015). Women were required to be continuously enrolled in TennCare during a baseline period encompassing the 180-day period before delivery through day 4 after delivery. To examine only opioid-naïve women during pregnancy, we excluded women with evidence of an opioid use disorder diagnosis (*International Classification of Diseases,* 9th edition (ICD9), codes 304.x, 304.7x, 305.5x, and 965.0), any filled prescription for buprenorphine or methadone, or more than one filled outpatient opioid prescription during the baseline period.

Women meeting all eligibility criteria entered the cohort on day 5 after delivery (to standardize the interval for identifying postpartum opioid prescriptions in the initial days after delivery). Follow-up continued through the earliest of the following: day 365 of follow-up after delivery, identification of a serious opioid-related event, loss of enrollment, or a non–opioid-related death (Supplementary Figure 1).

Exposure and Covariates

The exposure of interest was the dose of the first outpatient prescription fill for study opioids in the initial postpartum period, defined as day 3 before delivery through day 4 after delivery (Supplementary Figure 1). Prescription fills in the 3 days before delivery were included to account for women filling an opioid prescription in preparation for pain management after delivery. Study opioid analgesics included only oral formulations used for pain management (Supplementary Code File) (Osmundson et al., 2020). Opioid doses were calculated as the total morphine milligram equivalent (MME) dispensed (i.e., MME = [Strength per unit] × [Number of units] × [MME conversion factor]). We categorized women into mutually exclusive categories based on the quartile distribution of dose (no opioid; 1–99 MME; 100–149 MME; 150–199 MME; and ≥200 MME). Secondary analyses examined dose based on nine commonly observed dose modes and by accounting for dose in the model using a linear term, restricted cubic splines, and fractional polynomial terms.

We measured covariates in the baseline period (180 days before delivery through day 4 after delivery) using birth certificate information, coded diagnoses, and prescription fill information. Covariates included demographics, delivery hospital characteristics, conditions association with pain, comorbidities with contraindications to the use of nonsteroidal anti-inflammatory drugs, severe maternal morbidity, bilateral tubal ligation, perineal laceration, mental health conditions, and medication use (Supplementary Table 1) (Osmundson et al., 2020). A lack of evidence for a covariate meant that the individual did not have a history of that condition or use of that medication, and so this information was not considered missing.

Serious Opioid-related Events

The study outcome was a composite of events with the outcome date as the earliest date one of the following occurred: 1) development of persistent opioid use (filling ≥1 opioid prescriptions that cumulatively total >90 days within a 180-day interval without a supply gap >30 days), 2) evidence of opioid use disorder (filling a methadone or buprenorphine prescription or an opioid use disorder diagnosis [ICD9 coded diagnoses: 304.0X; 304.7X; 305.5X; 965.0]), 3) opioid-related overdose diagnosis (ICD9 coded diagnoses: 965.0X; E850.0-E850.2), or 4) opioid-related death (ICD10 coded underlying cause of death: T40.0-T40.4; X42; X62; Y12) (Osmundson et al., 2020). Outcomes identified using ICD9 coded diagnoses required that a coded diagnosis be identified from a hospitalization, a 23-hour stay, emergency department visit, or two outpatient encounters on separate dates. The outcome date for the development of persistent opioid use was the fill date of the prescription that met the greater than 90-day supply requirement.

Statistical Analysis

We used multivariable Cox proportional hazards models to compare the risk of developing a serious opioid-related event among women who filled an opioid prescription in one of four mutually exclusive dose categories (1–99, 100–149, 150–199, and ≥200 MME) compared with women who did not fill an opioid prescription in the initial postpartum period, accounting for relevant covariates. We calculated adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) using robust standard errors

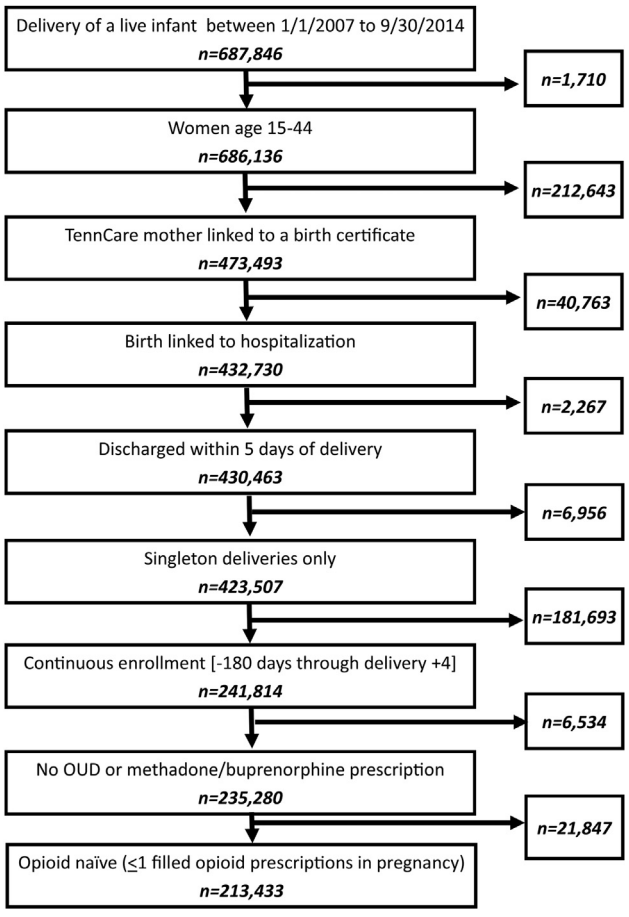

Figure 1. Flow diagram to identify retrospective cohort of women with one or more opioid prescriptions filled during pregnancy enrolled in Tennessee Medicaid at delivery (vaginal deliveries = 147,598; cesarean deliveries = 65,835; 2007–2015). OUD, opioid use disorder.

to account for women contributing more than one delivery to the cohort.

In a secondary analysis to allow for a nonlinear dose association, we modeled opioid dose as a categorical variable defined based on post hoc identification of nine commonly observed dose modes. Furthermore, to examine the effect of dose as a continuous measure, we plotted the marginal effect of dose on the relative hazard at prespecified dose values from Cox proportional hazards models that included dose as a linear term, restricted cubic splines and as a fractional polynomial (Kahan, Rushton, Morris, & Daniel, 2016; Steenland & Deddens, 2004). In each of the continuous models, we accounted for the effect of filling an opioid prescription due to the large percentage of women with vaginal deliveries who did not receive opioids (resulting in a spike-at-zero relative to opioid dose) (Lorenz, Jenkner, Sauerbrei, & Becher, 2019; Royston, 2013). In a sensitivity analysis, we examined only the most severe serious opioid-related events by recreating our analytical dataset excluding persistent opioid use from the outcome. In a separate sensitivity analysis, we restricted the population to women with a full year of enrollment before delivery to determine the impact of an expanded baseline period including time before pregnancy. Statistical analyses were completed using Stata, Version 16.1 (StataCorp LP, College Station, TX).

Results

Study Population

Of 213,433 women with one or fewer opioid fills during pregnancy and with continuous baseline enrollment before delivery through postpartum day 4, 69.2% ($n = 147,598$) underwent vaginal deliveries during the study period (2007–2015) (Figure 1). Of the 113,834 unique women in the study, 86,786 (76.2%), 21,557 (18.9%), and 5,491 (4.8%) contributed one, two, and three or more vaginal deliveries to the study population, respectively. The median age at delivery was 23 years and most women identified as White, non-Hispanic (60.7%) and reported at least one prior delivery (59.1%). More than one-half of the women with a vaginal delivery filled an initial postpartum opioid prescription (53.2%).

Women who filled any postpartum opioid prescription were more likely to be White compared with Black, Hispanic, and other, and to be from Central and East Tennessee compared with the West (Table 1). Across all opioid dose categories, there were modest differences in the prevalence of bilateral tubal ligation (8.9% of women in the ≥200 MME category; 3.4% in the 1–99 MME category; 1.3% in the no opioid category), whereas differences in tobacco use history, having one opioid prescription filled before delivery, and antidepressant use were only different among those who filled a postpartum opioid compared with those who did not (Table 1). Key demographic information was missing for a small subset of women (4.0%) who were excluded from subsequent analyses. Other characteristics of the retrospective cohort are presented in Supplementary Table 1.

Postpartum Opioid Use and the Risk of Serious Opioid-Related Events

Most women remained in the cohort through the end of 1 year of follow-up ($n = 95,739$ [67.5%]), although some lost enrollment ($n = 43,105$ [30.4%]) or experienced non–opioid-related deaths ($n = 59$ [0.04%]). The percentage of women who lost enrollment was higher among women filling a postpartum opioid prescription (32.5%) compared with women who did not fill a postpartum opioid prescription (27.9%). We observed 2,857 serious opioid-related events (incidence rate of 2.40 per 100 person-years). The earliest incident event for most women was persistent opioid use (65.6%) followed by an opioid use disorder diagnosis (20.4%) and filling a buprenorphine or methadone prescription (11.8%). We identified few opioid overdoses ($n = 59$ [2.1%]) and opioid-related deaths ($n = 4$ [0.1%]) that preceded other events.

In the analysis ($n = 141,760$) excluding women with missing birth certificate information (4.0% of vaginal deliveries), the rate of serious-opioid related events was significantly elevated regardless of the dose of the initial postpartum opioid used (any filled postpartum opioid prescription: 3.20 per 100 person-years; range of 2.94–3.61 per 100 person-years across dose categories) compared with women who did not fill an opioid prescription (1.51 per 100 person-years). After adjusting for all previously described covariates, compared with women who did not fill an opioid prescription, the average hazard ratio over time of serious-opioid related events was consistently and significantly higher among women across all dose categories (1–99 MME aHR, 1.52 [95% CI, 1.33–1.74]; 100–149 MME aHR, 1.41 [95% CI, 1.26–1.58]; 150–199 MME aHR, 1.40 [95% CI, 1.26–1.57]; and ≥200 MME aHR, 1.60 [95% CI, 1.43–1.78]) (Table 2 and

Table 1
Selected Baseline* and Follow-Up Characteristics of Women With Vaginal Delivery Stratified by Overall Opioid MME Quartiles of the First Postpartum Opioid Prescription, Tennessee Medicaid (2007–2015)

Characteristics	No Opioid	1-99 MME	100-149 MME	150-199 MME	≥200 MME
Total patients (*N*)	69,025	11,371	22,465	24,112	20,625
Follow-up					
Total, years	58,794	9,419	18,592	19,879	16,725
Mean follow-up, months	10.2	9.9	9.9	9.9	9.7
Age, years					
Mean ± standard deviation	23.6 ± 5.2	23.3 ± 4.8	23.3 ± 4.8	23.6 ± 5.0	23.7 ± 5.0
Median (interquartile range)	23 (7)	22 (6)	22 (6)	23 (6)	23 (7)
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Race/ethnicity					
White non-Hispanic	35,487 (51.4)	7,773 (68.4)	15,005 (66.8)	16,500 (68.4)	14,871 (72.1)
Black, Hispanic, other	33,484 (48.5)	3,595 (31.6)	7,449 (33.2)	7,602 (31.5)	5,743 (27.8)
Missing	54 (0.1)	3 (0.0)	11 (0.0)	10 (0.0)	11 (0.1)
Parity					
0	26,652 (38.6)	4,747 (41.7)	9,839 (43.8)	9,995 (41.5)	8,620 (41.8)
1	20,166 (29.2)	3,552 (31.2)	6,586 (29.3)	7,157 (29.7)	6,018 (29.2)
≥2	22,047 (31.9)	3,050 (26.8)	5,993 (26.7)	6,864 (28.5)	5,851 (28.4)
Missing	160 (0.2)	22 (0.2)	47 (0.2)	96 (0.4)	136 (0.7)
Region					
West	32,099 (46.5)	2,923 (25.7)	6,109 (27.2)	5,355 (22.2)	3,272 (15.9)
Central	17,598 (25.5)	3,896 (34.3)	7,171 (31.9)	10,302 (42.7)	10,400 (50.4)
East	19,028 (27.6)	4,526 (39.8)	9,145 (40.7)	8,409 (34.9)	6,935 (33.6)
Missing	300 (0.4)	26 (0.2)	40 (0.2)	46 (0.2)	18 (0.1)
Delivery complications					
Severe maternal morbidity†	681 (1.0)	97 (0.9)	189 (0.8)	225 (0.9)	195 (0.9)
Bilateral tubal ligation	909 (1.3)	389 (3.4)	644 (2.9)	1,334 (5.5)	1,826 (8.9)
Laceration	458 (0.7)	101 (0.9)	280 (1.2)	327 (1.4)	339 (1.6)
Comorbidities and medication use					
Tobacco use	14,185 (20.6)	3,434 (30.2)	6,279 (28.0)	7,179 (29.8)	6,379 (30.9)
Pre-delivery opioid use	7,506 (10.9)	1,640 (14.4)	3,222 (14.3)	3,841 (15.9)	3,159 (15.3)
Benzodiazepine use	1,170 (1.7)	337 (3.0)	509 (2.3)	704 (2.9)	651 (3.2)
Depression medication use	2,305 (3.3)	622 (5.5)	1,313 (5.8)	1,546 (6.4)	1,316 (6.4)
Depression diagnosis	1,307 (1.9)	245 (2.2)	552 (2.5)	518 (2.1)	389 (1.9)
Anxiety diagnosis	680 (1.0)	140 (1.2)	262 (1.2)	263 (1.1)	208 (1.0)
Bipolar diagnosis	813 (1.2)	153 (1.3)	258 (1.1)	321 (1.3)	263 (1.3)
NSAID contraindication	128 (0.2)	27 (0.2)	47 (0.2)	41 (0.2)	37 (0.2)
Surgical procedure	1,133 (1.6)	217 (1.9)	353 (1.6)	461 (1.9)	438 (2.1)
Trauma diagnosis	1,864 (2.7)	345 (3.0)	687 (3.1)	684 (2.8)	640 (3.1)
Musculoskeletal pain	2,862 (4.1)	720 (6.3)	1,062 (4.7)	957 (4.0)	905 (4.4)
Back pain	3,575 (5.2)	881 (7.7)	1,520 (6.8)	1,469 (6.1)	1,246 (6.0)
Arthritis pain	3,413 (4.9)	851 (7.5)	1,446 (6.4)	1,378 (5.7)	1,206 (5.8)
Malignancy	795 (1.2)	169 (1.5)	393 (1.7)	404 (1.7)	296 (1.4)
Headache	1,771 (2.6)	386 (3.4)	715 (3.2)	585 (2.4)	506 (2.5)
Hospitalizations in prior 6 months‡					
≤1	45,208 (65.5)	6,356 (55.9)	12,575 (56.0)	14,810 (61.4)	12,372 (60.0)
2	13,095 (19.0)	2,439 (21.4)	4,969 (22.1)	4,903 (20.3)	4,304 (20.9)
≥3	10,722 (15.5)	2,576 (22.7)	4,921 (21.9)	4,399 (18.2)	3,949 (19.1)
ED visits in prior 6 months‡					
0	38,976 (56.5)	6,606 (58.1)	13,447 (59.9)	13,534 (56.1)	11,902 (57.7)
1	16,772 (24.3)	2,930 (25.8)	5,582 (24.8)	6,070 (25.2)	5,013 (24.3)
≥2	13,277 (19.2)	1,835 (16.1)	3,436 (15.3)	4,508 (18.7)	3,710 (18.0)
Outpatient visits in prior 6 months‡,§					
0	19,855 (28.8)	2,576 (22.7)	5,276 (23.5)	5,830 (24.2)	5633 (27.3)
1–6	43,161 (62.5)	7,696 (67.7)	14,711 (65.5)	16,015 (66.4)	13,546 (65.7)
≥7	6,009 (8.7)	1,099 (9.7)	2,478 (11.0)	2,267 (9.4)	1,446 (7.0)

Abbreviations: MME, morphine milligram equivalent; NSAID, nonsteroidal anti-inflammatory drug.

* The distribution of additional characteristics is described in Supplementary Table 1. Baseline included covariates measured during pregnancy through day 4 after delivery.

† Individual categories for severe maternal morbidity included myocardial infarction, aneurysm, renal disease, acute respiratory distress syndrome, amniotic fluid embolism, liver disease, arrythmia, disseminated intravascular coagulation, eclampsia, heart failure, cerebrovascular accident, edema, anesthesia complication, sepsis, shock, sickle cell disease, embolism, transfusion, hysterectomy, tracheal intubation, cardiomyopathy, and ventilation.

‡ Categories created a priori based on the quartile distribution for each variable in the total population, although clustering at specific values led to only three categories for each variable.

§ Outpatient visits includes but is not limited to prenatal care visits.

Supplementary Table 2). Results were consistent in a regression model including an interaction between opioid dose and time to account for a minor violation of the proportional hazards assumption (Supplementary Table 3).

Secondary and Sensitivity Analyses

In comparison with not filling a postpartum opioid prescription, we noted an increased risk of serious opioid-related

Table 2
Crude and Adjusted HRs for SORE by Opioid MME Quartile Categories Among Women With Vaginal Deliveries (n = 141,598), Tennessee Medicaid (2007–2015)*[1]

MME Category	SORE	Follow-Up, Years	SORE/100 Person-years	Crude HR	95% Confidence Interval	Adjusted HR	95% Confidence Interval
No opioid	843	56,019	1.51	1.00	Reference	1.00	Reference
1–99 MME	303	9,098	3.33	2.22	(1.95–2.54)	1.52	(1.33–1.74)
100–149 MME	529	17,971	2.94	1.97	(1.76–2.19)	1.41	(1.26–1.58)
150–199 MME	599	19,162	3.13	2.09	(1.88–2.32)	1.40	(1.26–1.57)
≥200 MME	583	16,168	3.61	2.42	(2.17–2.69)	1.60	(1.43–1.78)

Abbreviations: HR, hazard ratios; MME, morphine milligram equivalents; SORE, serious opioid-related events.
* Distance to hospital and age were modeled as restricted cubic splines. All other covariates are modeled as categorical (parity, discharge year, region, income, health care use variables) or binary covariates. Patients with missing information in covariates were excluded.

events at all eight opioid dose categories (although the CIs for dose categories 85–95 and 125–145 MME included 1.0) (Figure 2). In the analysis incorporating opioid dose as a linear measure, after accounting for covariates and for filling an opioid prescription, the aHRs were significantly elevated at all dose values (Figure 3). Findings were similar in analyses using restricted cubic splines and fractional polynomial terms (data not shown).

In a sensitivity analysis among only women with continuous enrollment 1 or more years before delivery (n = 71,163), we observed a significantly increased risk of serious opioid-related events at all doses, similar to the primary analysis (1-99 MME aHR, 1.56 [95% CI, 1.25–1.96]; 100–149 MME aHR, 1.42 [95% CI, 1.18–1.72]; 150–199 MME aHR, 1.38 [95% CI, 1.15–1.66]; ≥200 MME aHR, 1.40 [95% CI, 1.15–1.70]). In a post hoc sensitivity analysis excluding women with bilateral tubal ligation, the results were nearly identical to the results from the primary analysis (1-99 MME aHR, 1.53 [95% CI, 1.34–1.76]; 100–149 MME aHR, 1.42 [95% CI, 1.27–1.60]; 150–199 MME aHR, 1.42 [95% CI, 1.27–1.58]; ≥200 MME aHR, 1.57 [95% CI, 1.39–1.76]).

In the sensitivity analysis excluding persistent use from the outcome, the rate of severe opioid-related events was 0.64 per 100 person-years among women who did not fill a postpartum opioid prescription compared with women who did (range, 1.02–1.24 per 100 person-years) (Supplementary Table 4). Compared with women who did not fill a postpartum opioid prescription, only those filling an opioid prescription for 200 or more MME had a statistically significant higher risk of developing an opioid use disorder, overdose, or opioid-related death after adjusting for relevant covariates (aHR, 1.31; 95% CI, 1.10–1.57). An exploratory sensitivity analysis examining opioid use disorder and overdose/opioid-related death separately produced similar findings.

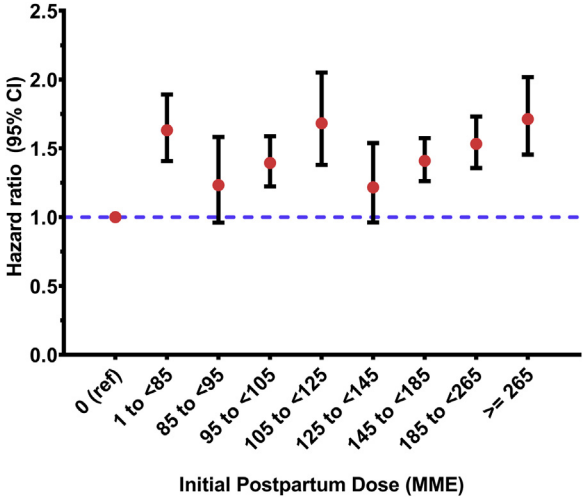

Figure 2. Adjusted hazard ratios for serious opioid-related events associated with the total dose of the first postpartum opioid prescription, compared with no postpartum opioid prescription, accounting for baseline comorbidities and medication use, delivery complications and multiple deliveries, Tennessee Medicaid (2007–2015). Red circles represent the hazard ratios at specific dose ranges (identified post hoc based on commonly observed modes); the black lines represent the 95% confidence interval (CI) for each hazard ratio; the blue dashed line represents a hazard ratio of 1.0. MME, morphine milligram equivalent.

Discussion

Compared with women who did not fill an opioid prescription, women who filled an opioid prescription after a vaginal delivery had an increased risk of serious opioid-related events, regardless of the dose. We observed similar findings when examining a categorical dose variable based on commonly observed modes, when modeling opioid dose as a continuous measure, and when incorporating a full one-year baseline period before birth. Thus, filling any dose of an opioid prescription after vaginal delivery was associated with an elevated risk of serious-opioid related events in the year after delivery.

Postpartum opioid prescribing among women after vaginal delivery is common in certain geographic regions and hospitals in the United States (Badreldin et al., 2018; 2019; Becker et al., 2018; Jarlenski et al., 2017; Osmundson et al., 2019; Prabhu et al., 2018; Schmidt et al., 2018). The previous literature regarding "safe" postpartum opioid doses have focused largely on the impact of opioids on lactation and safety concerns for the neonate (Darnall & Schatman, 2015; Fleet, Jones, & Belan, 2017; Hendrickson & McKeown, 2012; Seaton, Reeves, & McLean, 2007). Current guidelines provide limited evidence-based recommendations related to opioid use following uncomplicated vaginal deliveries (American College of Obstetricians and Gynecologists, 2018). In a retrospective cohort study of women enrolled in TennCare in which over half of women with a vaginal delivery filled an opioid in the 42-day postpartum period, the incidence of persistent opioid use was strongly associated with receiving a postpartum prescription within 7 days after delivery (adjusted risk ratio, 2.58; 95% CI, 1.80–3.71) and more strongly associated with receiving a postpartum prescription within 7 days and 8–42 days after delivery (adjusted risk ratio, 28.87; 95% CI, 20.37–40.91) (Osmundson et al., 2019). The number of filled opioid prescriptions in the 42-day postpartum period was also strongly associated with the risk of serious opioid-related events (persistent opioid use, opioid use disorder, overdose, and opioid-related death) (Osmundson et al., 2020). Among privately insured patients from a single U.S. health insurer, the risk of filling an opioid at 4 months or more after delivery was significantly higher among women prescribed opioids after cesarean delivery compared with women who were not prescribed

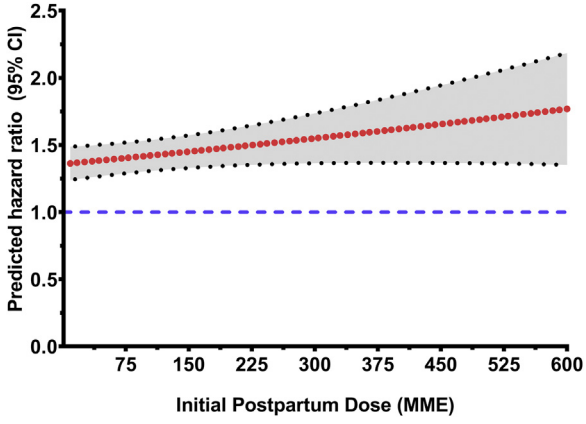

Figure 3. Adjusted hazard ratios for serious opioid-related events at selected values of the dose of the first postpartum opioid prescription (up to the 99th percentile: 600 MME) accounting for baseline comorbidities, medication use, delivery complications, and multiple deliveries, Tennessee Medicaid (2007–2015). The input in the figure is created using a Stata command (marginscontplot) that allows for the plotting of the marginal effect of a continuous variable on the relative hazard in a Cox model. We calculated these exponentiated linear predictions while setting the values of every other covariate to 0. MME, morphine milligram equivalent. (Royston P. marginscontplot: Plotting the Marginal effects of continuous predictors. 2013. *The Stata Journal*. 13(3):510–527. https://doi.org/10.1177/1536867X1301300305).

an opioid after vaginal delivery, a comparator selected to reflect baseline risk of chronic opioid use in the postpartum period (Bateman et al., 2016). Our findings build on this prior evidence by demonstrating that filling a single initial opioid prescription at any dose after a vaginal delivery is significantly associated with a risk of serious opioid-related events.

The number of pregnancy-related deaths involving opioids more than doubled from 2007 to 2016 (from 1.3 to 4.2 per 100,000 live births), constituting an increasing proportion of overall pregnancy-related deaths (from 4% to 10%) (Gemmill, Kiang, & Alexander, 2019). Persistent opioid use, new diagnoses of opioid use disorders, and nonfatal overdoses among pregnant and postpartum women are more common than opioid-related deaths, and they have also increased (Schiff et al., 2018). Many of these serious opioid-related events do not occur until well beyond the traditional 42-day postpartum period. In one study of fatal and nonfatal overdoses among pregnant and postpartum women, the overdose rate peaked in the 7–12 months after delivery (Schiff et al., 2018). Our findings highlight the imperative to investigate the consequences of postpartum opioid prescribing beyond the postpartum period.

Previous research examining opioid dose in nonobstetric populations has largely focused on the risk of opioid-related overdoses and deaths. Most of these studies modeled opioid exposure as a categorical variable and report higher risks of opioid-related death and overdose associated with higher average daily prescribed doses compared with prescribed doses of 1–19 MME per day (Dunn et al., 2010; Gomes, Mamdani, Dhalla, Paterson, & Juurlink, 2011; Turner & Liang, 2015; Zedler et al., 2014). Nevertheless, fewer studies have modeled opioid exposure continuously or accounted for patients who did not receive prescribed opioids. In a study of Veterans Health Administration patients prescribed opioids for chronic pain, overdose cases had a higher average prescribed dose compared with controls (98.1 MME/d vs. 47.7 MME/d) (Bohnert, Logan, Ganoczy, & Dowell, 2016). In a prospective observational cohort in North Carolina that linked prescribing information from a controlled substances monitoring database to state-specific mortality data, increasing daily doses were associated with an increasing risk of opioid-related overdose deaths in those prescribed 40.0 or more MME per day compared with those receiving more than 0 to 39.9 MME per day. In that study, not receiving any opioid prescription was protective (incidence rate ratio, 0.57; 95% CI, 0.44–0.73), and the increasing risk of opioid-related overdose leveled off at more than 200 MME per day (Dasgupta et al., 2016). Nevertheless, limited covariate information was available and control of potential confounding was challenging in that study. In our study, we observed a significantly increased risk of opioid use disorder, overdose, or opioid-related death within one year after delivery among women filling an opioid prescription with a total dose of 200 MME or more, although it is possible the induction period for more severe opioid-related events could be longer than 1 year among women filling a postpartum opioid at lower doses.

Although outpatient filled pharmacy data are reliable and free of recall issues, our study was limited by using the filled opioid dose as a proxy for opioid consumption. Furthermore, we could not observe actual medication use, illicit opioid use, or inpatient opioid use (Badreldin et al., 2018). Recent studies suggest that many women use less than the amount of opioid prescribed after cesarean delivery, although fewer data are available on actual use after vaginal delivery (Komatsu, Carvalho, & Flood, 2018; Komatsu et al., 2017; Nakahara, Ulrich, & Gala, 2018; Schmidt et al., 2018). The baseline period starting only 6 months before delivery in the primary analysis is another potential limitation as it may have been insufficient to identify all women with a history of opioid use disorder before pregnancy, although we did report similar findings in a sensitivity analysis extending the baseline to 12 months before delivery. Additionally, the restriction of follow-up at one year after delivery limited our ability to detect severe opioid-related events with longer potential induction periods after opioid initiation (i.e., opioid use disorder, overdose, and opioid-related death). Our analyses accounted for an extensive list of relevant covariates identified a priori and complemented claims data with data from birth certificates and a hospital discharge registry, but we cannot rule out the possibility of residual confounding, including confounding owing to the misclassification of covariates as a result of incorrect or incomplete diagnoses. Finally, though our findings may not be directly generalizable to privately insured women or women outside of Tennessee, these findings are important as the TennCare population represents more than 50% of all live births in the state of Tennessee and a number of other U.S. states are similarly affected by high postpartum opioid prescribing (Becker et al., 2018). Although the study period encompassed a time frame before the implementation of many current regulations aimed at reducing prescription opioid use, it is prudent to continue to evaluate optimal dose and use patterns. The study data were collected before these regulations and thus provided a wider range of exposure variability in which to examine these questions. Of note, the national burden of deaths associated with prescription opioids has remained consistently and substantially elevated through the end of 2018, the most recent data available (National Institute on Drug Abuse, 2020).

Implications for Practice and/or Policy

Best practices to manage pain after childbirth, especially for women with vaginal birth, remain unclear. Because postpartum opioid use can represent first exposure to potentially addictive

medications among reproductive-age women, judicious prescribing strategies are paramount (Dowell et al., 2016; Fraser & Plescia, 2019). Previous studies in nonobstetric populations have defined thresholds of inappropriate opioid prescribing associated with severe opioid-related events based on high daily opioid doses at levels greater than 50 MME per day (Dowell et al., 2016). Our study found a clinically relevant increased risk for women filling any postpartum opioid dose after vaginal delivery. Although general recommendations to prescribe the shortest reasonable duration at the lowest dose are still appropriate, our study was not able to identify a safe opioid dose. Because routine postpartum prescribing may represent provider preference rather than patient needs, revised guidelines should recommend against routine opioid prescribing to women with uncomplicated vaginal deliveries. Postpartum pain management should involve a shared decision between the woman and the provider and consider nonpharmacologic and nonopioid alternatives when appropriate (American College of Obstetricians and Gynecologists, 2018).

Conclusions

Filling an opioid prescription after a vaginal delivery is associated with an increased risk of serious opioid-related events among women without established opioid use during pregnancy, regardless of dose. Our findings raise serious concerns and support a call for additional scrutiny regarding the routine prescribing of opioids, even at low doses, after an uncomplicated vaginal delivery.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.whi.2021.03.002.

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Author Descriptions

Andrew D. Wiese, PhD, MPH, is an Assistant Professor in the Department of Health Policy at the Vanderbilt University. Dr. Wiese is a pharmacoepidemiologist whose research leverages observational studies to provide real-world evidence of the safety of commonly used medications.

Sarah S. Osmundson, MD, MPH, is an Associate Professor of Maternal-Fetal Medicine at VUMC whose research focuses on examining the safety of opioid prescribing after childbirth through both clinical trials and epidemiological data.

Edward Mitchel Jr., MS, is a data programmer in the Department of Health Policy, Vanderbilt University Medical Center.

Margaret Adgent, PhD, MSPH, is a research assistant professor in the Department of Health Policy at VUMC whose primary research interests focus on characterizing prenatal and pediatric exposures and their related health effects, particularly in the context of exploring developmental origins of disease.

Sharon Phillips, MSPH, is an Associate in Biostatistics in the Department of Biostatistics, Vanderbilt University Medical Center. She is a collaborative biostatistician with an interest in surgical outcomes, clinical trials, and female cancers.

Stephen W. Patrick, MD, MPH, MS, is the Director of the Vanderbilt Center for Child Health Policy, an Associate Professor of Pediatrics and Health Policy, and a practicing neonatologist at Vanderbilt University Medical Center. Dr. Patrick's research focuses on improving outcomes for pregnant women and infants affected by the opioid crisis.

Arlyn Horn, PharmD, MPH, was a community pharmacist at Affordable Pharmacy Services and a research assistant in the Department of Health Policy at Vanderbilt University Medical Center.

Lauren R. Samuels, PhD, is a Research Assistant Professor in the Department of Biostatistics at Vanderbilt University Medical Center. Dr. Samuels is a collaborative biostatistician working primarily in the areas of health services research and health policy.

Marie R. Griffin, MD, MPH, is professor emerita in the Department of Health Policy, Vanderbilt University Medical Center. She is a general internist and pharmacoepidemiologist whose research has involved the safety and effectiveness of drugs and vaccines, and the burden of vaccine-preventable diseases.

Carlos G. Grijalva, MD, MPH, is an Associate Professor in the Division of Pharmacoepidemiology, Department of Health Policy at VUMC whose research focuses on the evaluation of medications' safety and effectiveness; the design of observational studies; and methodologies for comparative effectiveness research.