

Patterns of Opioid Utilization in Pregnancy in a Large Cohort of Commercial Insurance Beneficiaries in the United States

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ABSTRACT

Background: There are few data regarding the utilization of opioids during pregnancy. The objective of this study was to define the prevalence and patterns of opioid use in a large cohort of pregnant women who were commercial insurance beneficiaries.

Methods: Data for the study were derived from a deidentified research database of women from across the United States who had both medical and prescription benefits. By using diagnostic codes, the authors defined a cohort of 534,500 women with completed pregnancies who were enrolled in a commercial insurance plan from 6 months before pregnancy through delivery.

Results: Overall, 76,742 women (14.4%) were dispensed an opioid at some point during pregnancy. There were 30,566 women (5.7%) dispensed an opioid during the first trimester, 30,434 women (5.7%) during the second trimester, and 34,906 women (6.5%) during the third trimester. Of these, 11,747 women (2.2%) were dispensed opioids three or more times during pregnancy. The most commonly dispensed opioids during pregnancy were hydrocodone (6.8%), codeine (6.1%), and oxycodone (2.0%). The prevalence of exposure at anytime during pregnancy decreased slightly during the study period from 14.9% for pregnancies that delivered in 2005 to 12.9% in 2011. The prevalence of exposure varied significantly by region and was lowest in the Northeast and highest in the South.

Conclusions: This study demonstrates that opioids are very common exposures during pregnancy. Given the small and inconsistent body of literature on their safety in pregnancy, these findings suggest a need for research in this area. (**ANESTHESIOLOGY 2014; XXX:XX-XX**)

APPROXIMATELY 2% of the U.S. adult population use opioids regularly,¹ and 10 to 30% of patients with chronic noncancer pain are treated with opioids.² Throughout the 1990s and early 2000s, the prescription of opiate pain medications increased two- to three-fold in the United States³⁻⁵ though it may have stabilized in recent years. Despite the importance of these medications for pain control and their potential for adverse effects, there are very few data regarding their use in pregnancy in the United States.^{6,7}

Although nearly all women will experience some pain during the course of pregnancy, the safety of using opioids to manage pain in pregnancy remains ill-defined. Some studies have reported an association between opioid use in the first trimester and major congenital malformations, but the findings vary.⁸⁻¹⁶ When opioids are used for extended courses during pregnancy, there is a known potential for neonatal opioid dependence and subsequent withdrawal symptoms in the first

What We Already Know about This Topic

- Opioid prescribing has increased in the United States, with approximately 2% of the population regularly using prescription opioids
- In contrast to the general population, opioid use during pregnancy has been little studied

What This Article Tells Us That Is New

- In a review of over 500,000 women enrolled in an insurance plan from 6 months before pregnancy through parturition, 14% received at least one dose of an opioid during pregnancy
- Over 1 in 20 women received an opioid during the first trimester, and prevalence of opioid exposure varied several-fold across states, being generally lowest in the Northeast and highest in the South

few days of life,¹⁷ but other potential consequences for the infants of long-term maternal opioid users are less clear.

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Defining how commonly opioids are prescribed in pregnancy, which opioids are preferred by physicians, what pain conditions are most frequently treated, and how patients who are chronically using opioids before pregnancy are managed during pregnancy are important in defining research priorities in this field. We therefore undertook a study to define patterns of utilization of opioids during pregnancy in a large cohort of pregnancies in the United States.

Materials and Methods

Definition of Cohort

Data for the patients included in this study came from a de-identified research database InVision for Data Mart, a product of OptumInsight Life Sciences (Eden Prairie, MN). It contains compiled membership and reimbursement transactions from a nationwide U.S. health insurer for employed people and their dependents who had both medical and prescription benefits. At the time evaluated in this study (between 2005 and 2011), the research database included claims for reimbursement of pharmacy dispensings, inpatient and outpatient services, and procedures (including associated diagnoses) for an open cohort with approximately 30% annual turnover, leading to an average cohort residence time of 2.48 yr (SD, 2.36) and a cross-sectional size that ranged from 12,750,397 to 14,483,016 persons depending on the study year (approximately 4% of the U.S. population). Demographics of people in the database are similar to the U.S. population for all ages less than 65 although the geographic distribution reflects the region-specific market-share of the insurer rather than the density of the underlying population. The pharmacy benefit of the health insurer is based on an open formulary with a tiered copayment structure that incentivizes preferred medications.

The study cohort was first defined on the basis of inpatient or outpatient codes indicating infant delivery using an algorithm based on *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic and procedure codes.¹⁸ We further refined the date of delivery for each pregnancy hierarchically based on either (1) delivery procedure codes, (2) the date of admission for the delivery, or (3) the date of the last outpatient visit with codes for delivery. The last menstrual period (LMP) was defined as 245 days before the date of delivery if the maternal record indicated that the delivery was preterm, otherwise the LMP was assigned as 273 days before delivery.¹⁹ Analyses were restricted to patients with continuous insurer enrollment from 180 days before the estimated LMP through date of delivery, allowing for up to 30-day lapses in coverage (534,500 completed pregnancies). No further restrictions or exclusions were imposed.

Definition of Pregnancy Periods and Exposure

We examined patterns of dispensing by type of opioids in the prepregnancy period, during each trimester, and then in pregnancy overall. The prepregnancy period represented two

consecutive 90-day periods before the estimated LMP. The first trimester extended from the estimated LMP through day 90 of pregnancy, second trimester was the after 90 days, and the third trimester began 181 days after estimated LMP and continued to delivery. Dates of pharmacy dispensing and expected duration of use based on days supplied for study medications were used to estimate duration of exposure during pregnancy.

The opioids considered in our analysis included hydrocodone, codeine, oxycodone, propoxyphene, tramadol, meperidine, hydromorphone, morphine, fentanyl, buprenorphine, methadone, pentazocine, tapentadol, and oxymorphone. In this analysis, we allowed days supply to accumulate for patients who were dispensed opioids before the days supply from their previous dispensing was expected to be completed. We assumed continuous exposure for patients with sequential prescriptions when the days supply expired less than 7 days before a new prescription. We also determined the mean number of dispensings, by type, for patients who were exposed to opioids during pregnancy.

Statistical Analyses. Analyses of patterns of dispensing, associated conditions, and temporal trends were descriptive of this commercially insured population. The results are parameters for this particular population rather than estimates based on samples. Accordingly, we present the results without confidence intervals.

Defining Patterns of Opioid Utilization in Prepregnancy Chronic Opioid Users

We defined chronic opioid users as women who received dispensings of an opioid during 3 or more separate months in the 180 days before pregnancy and then examined patterns of opioid dispensing during the first and second trimesters for this group. We identified, by trimester, those who were dispensed the same type of opioid, dispensed a different type of opioid, or were not dispensed any opioid.

Description of Associated Conditions

Medical conditions that might be associated with opioid prescription were identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes in the patients' inpatient and outpatient records between 180 days before LMP and delivery. The frequency of each of these conditions was determined in (1) all patients exposed to opioids during pregnancy, (2) patients with three or more dispensings of opioids during pregnancy, (3) patients who were defined as chronic users before LMP, and (4) patients who were unexposed to opioids during pregnancy.

Temporal and Regional Trends in Utilization of Opioids during Pregnancy

For each year in the study period (defined by the year of delivery), we examined the frequency of exposure to any opioids at anytime during pregnancy and during each of the three trimesters observed. We also examined trends in the

frequency of exposure to the four most commonly dispensed opioids at any time during pregnancy.

We examined regional variations in opioid prescribing using a mixed-effects logistic regression model to account for random variation. The state identifier was modeled as a normally distributed random intercept. Each intercept represents the state-specific prescribing rate, defined as the proportion of pregnant women who were dispensed opioid medications at any time during pregnancy. These predicted state-specific prescribing rates are empirical Bayes estimates; that is, they have been shrunk toward the overall mean prescribing rate.²⁰

All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). The use of this deidentified database for research was approved by the Partners Institutional Review Board (Boston, Massachusetts).

Results

There were 534,500 completed pregnancies eligible for analysis (meeting criteria of enrollment in the health insurer from 6 months before pregnancy through delivery). The median age of the women at the time of delivery was 31 yr (interquartile range, 28 to 35); 17,793 (3.3%) pregnancies were multiple gestations and 37,795 (7.1%) were preterm deliveries. There were 59,405 (11.1%) pregnancies from the Northeast, 230,137 (43.1%) from the South, 147,137 (27.5%) from the Midwest, and 97,771 (18.3%) from the West. There were 435,649 women who had one pregnancy during the study period, 45,389 who had two pregnancies, and 2,656 who had three or more pregnancies.

Overall, 76,742 women (14.4%) were dispensed an opioid at some point during pregnancy. Exposure occurred in 30,566 women (5.7%) during the first trimester, in 30,434 women (5.7%) during the second trimester, and in 34,906 women (6.5%) during the third trimester (table 1). When we excluded prescriptions filled within 3 days of delivery (and thus potentially in anticipation of the need for post-operative analgesia after a cesarean delivery or the like), the prevalence of exposure in the third trimester decreased only slightly to 6.2%. The frequency of exposure during each of these periods was considerably lower than the frequency of exposure during the two 90-day periods that preceded pregnancy (10.0 and 9.7%, respectively). There were 11,747 women (2.2%) who were dispensed opioids three or more times during pregnancy. Of the 76,742 women exposed to opioids during pregnancy, 7,135 (9.3%) had a hospital admission with a primary procedure code indicating that they underwent a surgical procedure. The frequency of opioid exposure in the first pregnancies recorded in the database was 14.4%, in the second pregnancy was 14.1%, and in the third or greater pregnancy was 14.9%.

The most common opioid dispensed in pregnancy was hydrocodone (dispensed to 6.8% of pregnant women), followed by codeine (6.1%), oxycodone (2.0%), and propoxyphene (1.6%). The distribution of opioid types dispensed was fairly uniform across the three trimesters (table 1).

Table 2 shows the mean, median, and interquartile range for the cumulative number of days supply during pregnancy for patients dispensed each type of opioids during pregnancy. For the most commonly used opioids (hydrocodone, codeine, oxycodone, and propoxyphene), the median

Table 1. Prevalence of Opioid Dispensing before and during Pregnancy

| | Exposure Window | | | | | |
|-----------------|-----------------------|-----------------|-----------------|------------------|-----------------|--------------------------|
| | -180 days to -91 days | -90 days to LMP | First Trimester | Second Trimester | Third Trimester | Anytime during Pregnancy |
| | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) |
| Any opioid | 53,587 (10.03) | 51,595 (9.65) | 30,566 (5.72) | 30,434 (5.69) | 34,906 (6.53) | 76,742 (14.36) |
| Specific opioid | | | | | | |
| Hydrocodone | 30,131 (5.64) | 29,712 (5.56) | 15,906 (2.98) | 12,879 (2.41) | 15,079 (2.82) | 36,234 (6.78) |
| Codeine | 10,692 (2.00) | 10,516 (1.97) | 9,347 (1.75) | 12,972 (2.43) | 13,949 (2.61) | 32,755 (6.13) |
| Oxycodone | 9,755 (1.83) | 8,509 (1.59) | 3,795 (0.71) | 3,718 (0.70) | 4,962 (0.93) | 10,402 (1.95) |
| Propoxyphene | 6,083 (1.14) | 5,674 (1.06) | 3,014 (0.56) | 2,980 (0.56) | 3,424 (0.64) | 8,347 (1.56) |
| Tramadol | 3,109 (0.58) | 3,306 (0.62) | 1,695 (0.32) | 742 (0.14) | 857 (0.16) | 2,526 (0.47) |
| Meperidine | 507 (0.09) | 563 (0.11) | 284 (0.05) | 282 (0.05) | 352 (0.07) | 853 (0.16) |
| Hydromorphone | 242 (0.05) | 222 (0.04) | 144 (0.03) | 184 (0.03) | 267 (0.05) | 512 (0.10) |
| Morphine | 197 (0.04) | 190 (0.04) | 149 (0.03) | 148 (0.03) | 186 (0.03) | 299 (0.06) |
| Fentanyl | 174 (0.03) | 177 (0.03) | 162 (0.03) | 138 (0.03) | 143 (0.03) | 249 (0.05) |
| Buprenorphine | 151 (0.03) | 176 (0.03) | 170 (0.03) | 134 (0.03) | 131 (0.02) | 209 (0.04) |
| Methadone | 116 (0.02) | 129 (0.02) | 125 (0.02) | 107 (0.02) | 115 (0.02) | 180 (0.03) |
| Pentazocine | 41 (0.01) | 35 (0.01) | 20 (0.00) | 22 (0.00) | 18 (0.00) | 49 (0.01) |
| Tapentadol | 20 (0.00) | 30 (0.01) | 12 (0.00) | 11 (0.00) | 17 (0.00) | 35 (0.01) |
| Oxymorphone | 26 (0.00) | 24 (0) | 31 (0.01) | 26 (0.00) | 27 (0.01) | 49 (0.01) |

LMP = last menstrual period.

Table 2. For Opioids Dispensed during Pregnancy, the Number of Days of Exposure Overlapping with Pregnancy by Type

| | Days of Exposure during Pregnancy | | | | Distinct Prescriptions |
|---------------|-----------------------------------|--------|-----------------|-----------------|------------------------|
| | Mean, SD | Median | 25th Percentile | 75th Percentile | Mean, SD |
| Hydrocodone | 15.2±36.5 | 5 | 3 | 10 | 1.9±2.8 |
| Codeine | 7.3±12.4 | 5 | 3 | 8 | 1.3±1.2 |
| Oxycodone | 18.9±46.9 | 4 | 3 | 9 | 2.0±2.9 |
| Propoxyphene | 9.1±18.6 | 5 | 3 | 8 | 1.4±1.4 |
| Tramadol | 32±52.6 | 10 | 5 | 30 | 2.3±3.6 |
| Meperidine | 7.8±14.1 | 5 | 3 | 7 | 1.3±1.3 |
| Hydromorphone | 19.7±41.5 | 5 | 3 | 14 | 1.9±2.0 |
| Morphine | 84.2±92.4 | 32 | 14 | 146 | 4.3±4.9 |
| Fentanyl | 105.4±93.2 | 71 | 30 | 199 | 4.8±5.1 |
| Buprenorphine | 131.6±98.7 | 116 | 30 | 235 | 6.5±5.3 |
| Methadone | 118.9±95.9 | 94 | 30 | 209 | 5.2±4.1 |
| Pentazocine | 24.3±47.2 | 7 | 3 | 22 | 1.8±1.8 |
| Tapentadol | 28.7±45.2 | 11 | 7 | 30 | 1.7±1.5 |
| Oxymorphone | 88.3±88.2 | 45 | 29 | 141 | 4.2±3.9 |

duration of exposure was less than a week. In contrast, morphine, fentanyl, buprenorphine, methadone, and oxymorphone were associated with longer durations of exposure. The number of distinct dispensings for each opioid also followed this pattern.

There were 5,838 patients chronically filling opioid prescriptions before pregnancy. Figure 1, A and B, shows patterns of opioid dispensing during the first and second trimesters, respectively, for patients who were chronically exposed to opioids before pregnancy (note, patients can belong to more than one group if they are chronically taking more than one type of opioid before pregnancy). Depending on the type, between 67 and 95% of chronic users were dispensed an opioid during the first trimester, with the majority being dispensed the same opioid that they used during the prepregnancy period, but between 8 and 15% were dispensed a different opioid. The frequency of opioid dispensing to chronic prepregnancy users generally declined in the second trimester and ranged from 53 to 90%. The proportion that was dispensed a different opioid than during the prepregnancy period ranged from 11 to 28% depending on the type.

Table 3 shows conditions present in patients with any opioid dispensing during pregnancy, patients with three or more dispensings of opioids during pregnancy, patients defined as chronic users before pregnancy, and in women unexposed during pregnancy. Back pain was the most commonly associated condition and was present in 37% of patients dispensed an opioid during pregnancy and 61% of those dispensed opioids three or more times during pregnancy. Other conditions that were most commonly associated with opioid exposure included abdominal pain, migraine, joint pain, and fibromyalgia.

Figures 2 and 3 show temporal trends in the utilization of opioids in pregnancy. As shown in figure 2, the prevalence of exposure at anytime during pregnancy decreased slightly

from 14.9% for pregnancies that delivered in 2005 to 12.9% in 2011. This decrease was noted in prevalence of exposure in each of the trimesters as well. Among the four most commonly dispensed opioids (fig. 3), there was a decrease in the use of codeine (from 7.2 to 5.3%), an increase in the use of oxycodone (from 1.6 to 2.1%), and relative stability in the use of hydrocodone. There was a notable decrease in the use of propoxyphene among pregnancies that delivered in 2011, reflecting the removal of propoxyphene from the market in the United States in late 2010.

Figure 4 shows the prevalence of opioid exposure at any point during pregnancy by state while accounting for random variation. Given the large number of pregnancies contributed by each individual state, the predicted prescribing based on the mixed-effects regression analysis was very similar to the actual observed prescribing for most states. Significant regional differences were observed. Use ranged between 6.5 and 26.3%. In general, the prevalence was lowest in the Northeast and highest in the South. Arkansas, Mississippi, and Alabama all had prevalences in excess of 20%. There was approximately a two-fold difference in the average prescribing rate of states in the lowest (10.2%) versus the highest (20.0%) prescribing quartile.

Discussion

In this analysis of over a half a million pregnancies among private health insurance beneficiaries drawn from across the United States from 2005 to 2011, we found that opioids were dispensed to 14% of women during the antepartum period with approximately 6% of women receiving opioids during each of the three trimesters. Although most opioid exposure represented short courses of treatment, 2.2% of women received three or more opioid dispensings during pregnancy. The most frequently prescribed opioids in pregnancy included hydrocodone, codeine, and oxycodone. The overall prevalence of exposure at any time during pregnancy,

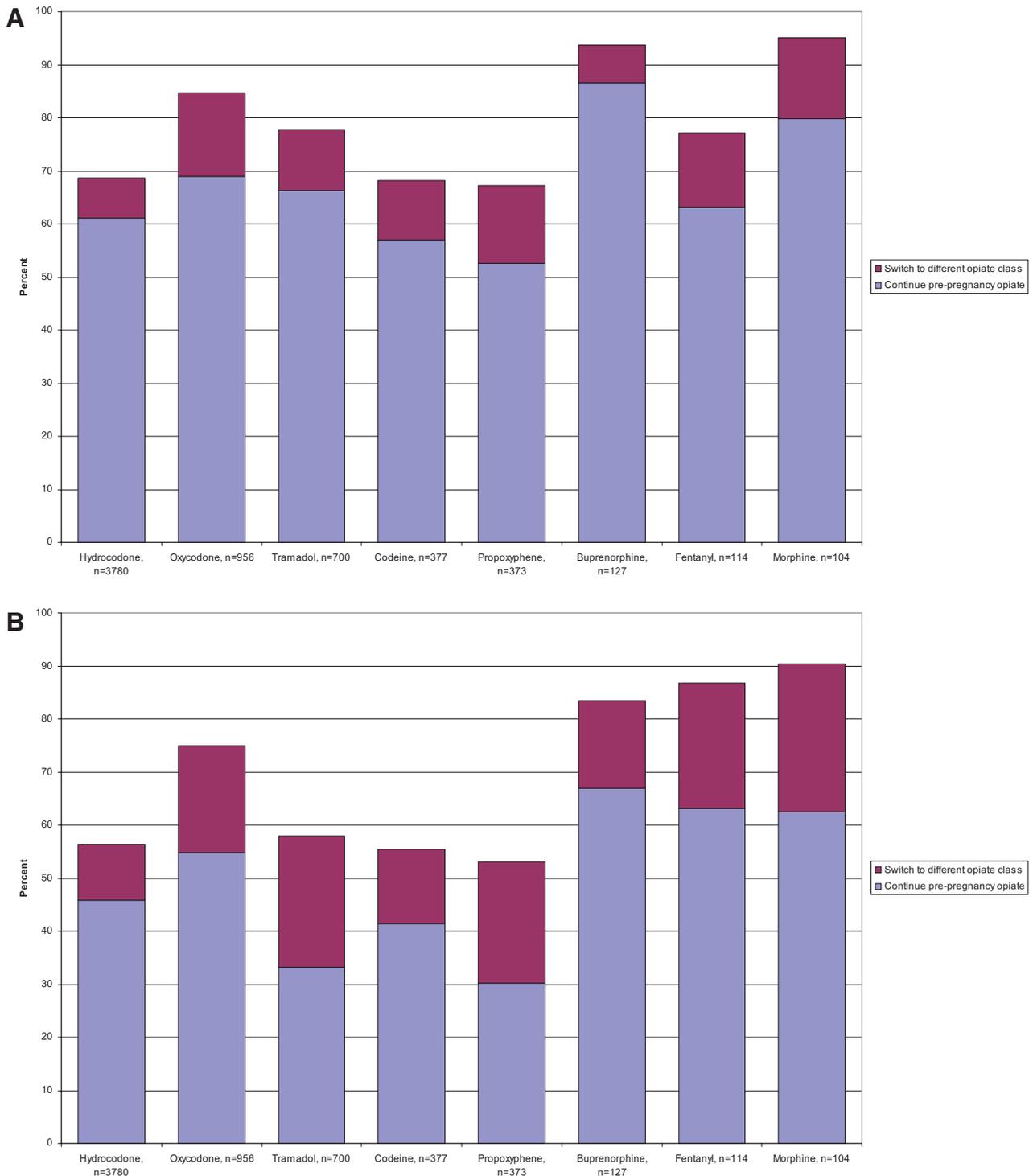


Fig. 1. Among patients chronically taking opioids before pregnancy (n = 5,838), patterns of opioid dispensing during (A) the first trimester and (B) the second trimester. Analysis restricted to types of opioids with greater than 100 prepregnancy chronic users.

while declining slightly, was in excess of 12% for each of the 7 yr in the study period.

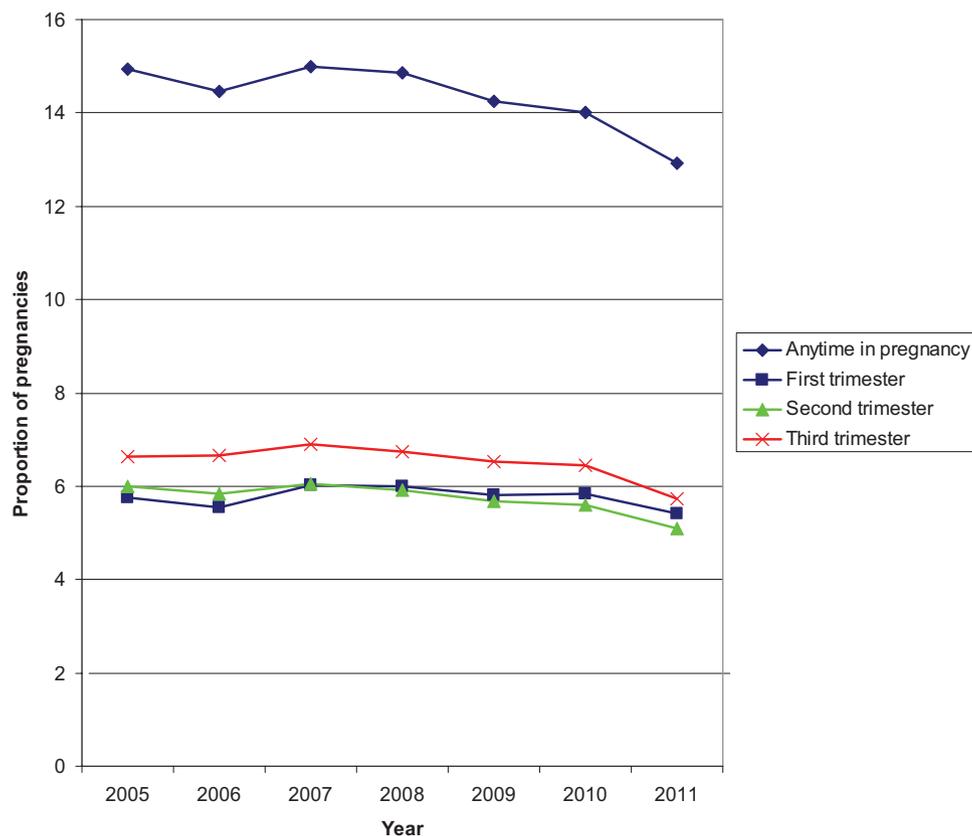
Although the risk of neonatal opioid dependence associated with prolonged opioid exposure is clear,²¹ other risks associated with opioid exposure remain ill-defined. The Collaborative Perinatal Project reported an increased risk of respiratory malformations associated with codeine, but

not with hydrocodone, meperidine, methadone, morphine, or oxycodone.⁸ Associations between first trimester exposure to codeine and cardiovascular defects were suggested in some case-control studies not specifically designed to study opioids,⁹⁻¹² and another study found an increased risk of oral clefts.¹³ In 2011, the National Birth Defects Prevention Study reported that opioid treatment (mainly

Table 3. Recorded Maternal Conditions, Stratified by Opioid Exposure during Pregnancy

| | Exposed to Opioids during Pregnancy (n = 76,742) | Three or more Dispensings of Opioids during Pregnancy (n = 11,747) | Chronic Users before LMP (n = 5,838) | Unexposed to Opioids during Pregnancy (n = 457,758) |
|--|--|--|--------------------------------------|---|
| | N (%) | N (%) | N (%) | N (%) |
| Back pain | 28,189 (36.7) | 7,160 (61.0) | 3,956 (67.8) | 84,003 (18.4) |
| Abdominal pain | 24,515 (31.9) | 5,025 (42.8) | 2,414 (41.3) | 70,415 (15.4) |
| Migraine | 7,817 (10.2) | 2,542 (21.6) | 1,264 (21.7) | 12,819 (2.8) |
| Joint pain | 9,258 (12.1) | 2,712 (23.1) | 1,623 (27.8) | 24,499 (5.4) |
| Fibromyalgia and or pain in multiple sites | 4,690 (6.1) | 1,559 (13.3) | 1,038 (17.8) | 12,939 (2.8) |
| Cough | 8,521 (11.1) | 1,682 (14.3) | 820 (14.0) | 21,585 (4.7) |
| Myalgia | 4,696 (6.1) | 1,560 (13.3) | 1,039 (17.8) | 12,973 (2.8) |
| Malignancy | 1,200 (1.6) | 316 (2.7) | 155 (2.7) | 4,617 (1.0) |
| Renal calculus | 3,217 (4.2) | 914 (7.8) | 315 (5.4) | 2,872 (0.6) |
| Rheumatoid arthritis | 613 (0.8) | 238 (2.0) | 168 (2.9) | 1,622 (0.4) |
| Opioid dependence | 422 (0.5) | 335 (2.9) | 280 (4.8) | 185 (0.0) |
| Other headache syndromes | 7,967 (10.4) | 73 (0.6) | 38 (0.7) | 22,790 (5.0) |
| Opioid abuse | 123 (0.2) | 90 (0.8) | 66 (1.1) | 68 (0.0) |
| Sickle cell anemia | 87 (0.1) | 22 (0.2) | 13 (0.2) | 373 (0.1) |
| Peripheral neuropathy | 66 (0.1) | 40 (0.3) | 27 (0.5) | 71 (0.0) |
| Chronic pancreatitis | 63 (0.1) | 29 (0.2) | 22 (0.4) | 66 (0.0) |

LMP = last menstrual period.

**Fig. 2.** Temporal trends in opioid dispensing during pregnancy (overall) and by trimester.

codeine and hydrocodone) early in pregnancy is associated with greater risk of cardiac septal defects, hypoplastic left heart syndrome, spina bifida, and gastroschisis.¹⁴ A recent

study from the Slone Epidemiology Center Birth Defects Study found an approximately two-fold increased risk of neural tube defects in association with periconceptual

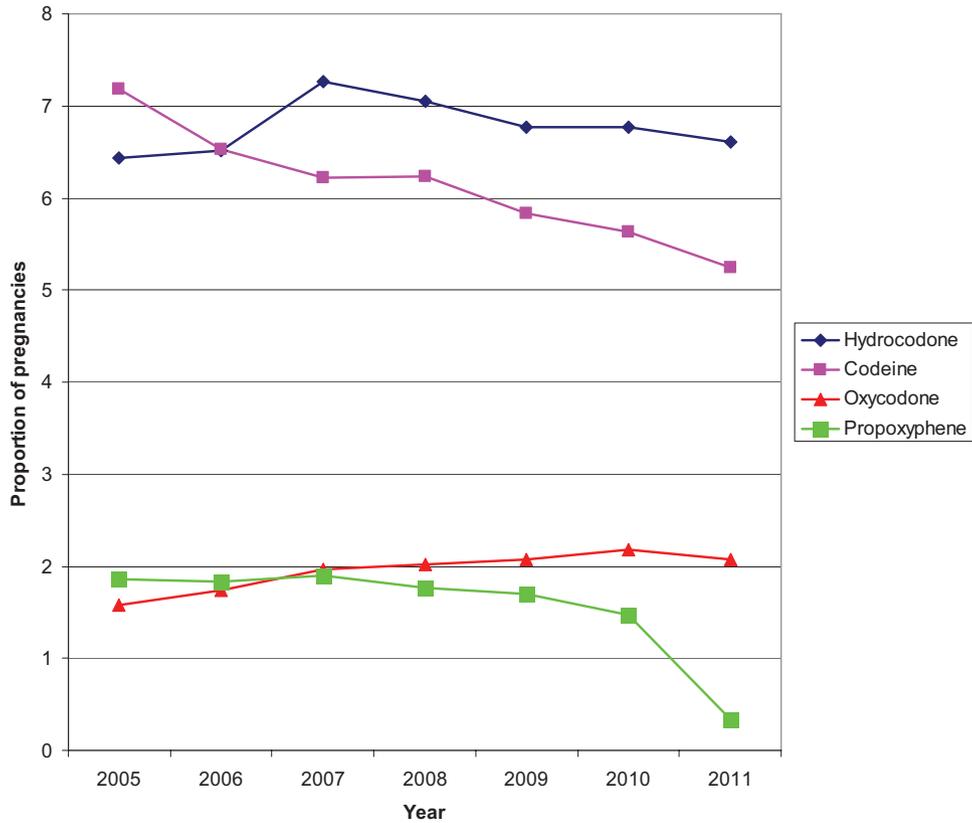


Fig. 3. Temporal trends in opioid dispensing during pregnancy for the four most commonly prescribed types.

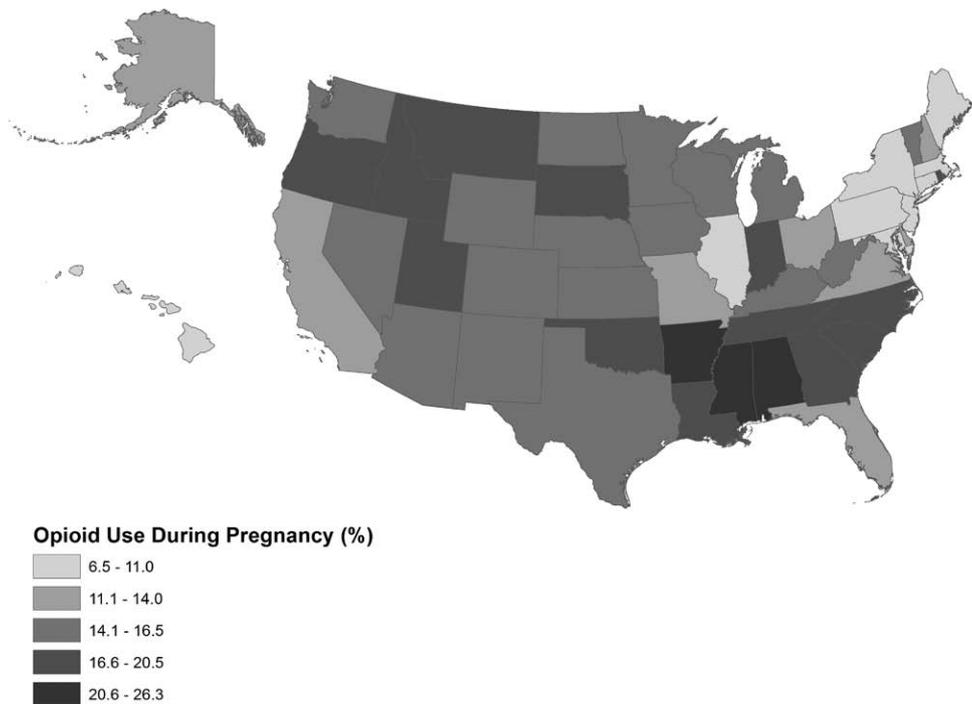


Fig. 4. Prevalence of opioid dispensing during pregnancy (overall) by state.

opioid use.¹⁶ However, an increased risk of malformations was not observed in a recent large European cohort study.¹⁵ Chronic opioid use in pregnancy has also been associated

with cesarean delivery, excessive postpartum hemorrhage due to uterine atony,¹⁵ low birth weight, fetal growth restriction, and other adverse neonatal outcomes. This

evidence regarding teratogenesis and other risks, in addition to being inconsistent, is limited by small numbers and multiple comparisons (increasing the probability of chance findings). Our data demonstrate that opioids are widely used in pregnancy, including during the first trimester where even a brief course could confer risk of teratogenesis.^{8–16} This suggests a need to better define the safety of opioid medications during pregnancy.

Pain syndromes, most frequently back pain, abdominal pain, joint pain, and headaches, are very common in pregnancy. Alternatives to opioids for the treatment of pain, most notably the nonsteroidal anti-inflammatory drugs, also have potential safety concerns associated with their use in pregnancy.²² Thus, there is need for comparative safety and effectiveness research to determine the optimal approach to the treatment of painful conditions in pregnancy. Likewise, it will be important to develop evidence for the safest approach for treating perioperative pain in pregnant women, as up to 2% of pregnant women will undergo nonobstetric surgery.²³

When we examined patterns of management of opioids for patients who were chronically taking opioids before pregnancy, it was notable that substantial fractions of women continued them into the second trimester. Thus, the majority of women who are taking opioids chronically before pregnancy continue to do so once they become pregnant. Given the known adverse effects of prolonged exposure to opioids on the fetus, our findings suggest that it is challenging for women on these medications chronically to discontinue their use during pregnancy. This further underscores the importance of evaluating the comparative safety of treatment alternatives to inform the treatment decision for women who require continued treatment during pregnancy.

The prevalence of exposure that we report is significantly higher than what has been observed in studies in European populations during a similar time frame.^{24,25} A population-based cohort study using the Norwegian Prescription Database linked to the Medical Birth Registry reported that 2.9% of women were exposed to opioids at any time during pregnancy during 2004 to 2008, compared with 14.4% in our study. This lower use was observed during all time periods: 2.6% during the 3 months before pregnancy, 1.4% during the first trimester, and 1.0% each during the second and third trimesters (*vs.* 9.7, 5.7, 5.7, and 6.5%, respectively, in our study). Prescription of opioids during pregnancy thus seems to be four to six times higher in the United States compared with prescription in Norway.²⁵ Furthermore, there were significant regional differences in the frequency of opioid exposure in our study, with several states in the South having prevalences in excess of 20%.

The number of opioid prescriptions issued nationwide has increased from 131 million in 2000 to 219 million in 2011, representing a 67% increase. The corresponding increase

during our 2005 to 2011 study period was 30%. During this same time period, there was a four-fold increase in the number of deaths related to opioid use.²⁶ Although it is perhaps encouraging that the overall prevalence of opioid exposure during pregnancy decreased slightly during the study period (from 14.9% in 2005 to 12.9% in 2011), the overall prevalence of exposure at the most recent estimate remains extremely high relative to what was observed in the European population. Our data therefore suggest that the epidemic of opioid overutilization in the United States that is known to exist in the general population extends to pregnancy.

Our study is subject to certain limitations. Although our data are drawn from claims of a private health insurer that includes beneficiaries from across the United States, a substantial fraction of deliveries in the United States occur to patients who are covered by Medicaid²⁷; it is unclear whether our findings are generalizable to these patients. As a consequence, the state-specific prescribing patterns only reflect those of the commercially insured population under study and cannot be used to extrapolate to the frequency of opioid exposure in the general obstetric population. In addition, our measure of exposure is based on pharmacy dispensing of medications, and not whether the medication was actually taken by the women. In light of the ongoing debate about opioid overprescribing, we recognize a value in documenting the prescribing patterns themselves during pregnancy. Of course, this analysis does not include exposure to opioids that are obtained illicitly. Accounting for such illicit exposure to opioids in pregnancy (or in the general population) would be a challenge for any study, irrespective of its data source or design. We also would not capture exposure to methadone at free-standing clinics. Furthermore, the health insurer database does not include most of the medications received by patients while hospitalized, which would lead to some degree of underestimation of opioid exposure in our study, especially because women might be in greater need of analgesics during a hospital stay. Our analysis is performed at the level of individual pregnancies, not women. This approach was taken as the effects of opioid exposure are likely most significant for the individual fetuses which are exposed *in utero*. Although this may lead to correlated exposures in individual women who had more than one pregnancy included in the analysis, we found a similar frequency of exposure in first pregnancies (14.4%), second pregnancies (14.1%), or third or greater pregnancies (14.9%). Finally, when using insurance claims data to study exposures during pregnancy, the LMP needs to be imputed based on claims for preterm labor and delivery. Although this approach has been shown to result in generally accurate estimation of gestational age,¹⁹ some degree of misclassification is likely.

In conclusion, the use of opioid analgesics in pregnant women in the United States is high and is dominated by treatments of short duration. The proportion of women exposed is relatively stable across trimesters and over time. Given this continued high use during all phases of pregnancy

and the small and inconsistent body of literature on their safety, there is a need for research on the comparative safety of these medications during pregnancy to help inform clinical practice and treatment guidelines.

Acknowledgments

Research reported in this publication was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health (Bethesda, Maryland) under Award Number K08HD075831 (to Dr. Bateman). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing Interests

Dr. Hernandez-Diaz has consulted for Novartis, GlaxoSmithKlein-Biologics (Middlesex, United Kingdom), and AstraZeneca (London, United Kingdom), and Dr. Seeger is a consultant to Optum Insight (Eden Prairie, Minnesota) and World Health Information Science Consultants, LLC (Newton, Massachusetts), both for unrelated projects. The other authors declare no potential conflict of interest.

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